IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

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GALDERMA LABORATORIES, L.P. and TCD ROYALTY SUB LP	:	Civil Docket 21-CV-1710
	:	Trial Day One
V.	:	Morning Session
	:	
LUPIN INC. and LUPIN LIMITED	:	Civil Bench Trial

BEFORE THE HONORABLE STEPHANOS BIBAS

James A. Byrne U.S. Courthouse
601 Market Street
Philadelphia, PA 19106
January 9, 2024 at 8:30 a.m.

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07:48:58AM 1 (Tuesday, January 9, 2024 at 8:30 a.m.)
08:29:35AM 2 THE COURT: Good morning. This is the United States
08:29:54AM 3 District Court for the District of Delaware. And we're in Case
08:30:00AM 4 Number 21-CV-1710. Galderma Laboratories versus Lupin.
08:30:07AM 5 Plaintiffs' counsel, please enter your appearances.
08:30:13AM 6 MR. TIGAN: Good morning, Your Honor. My name is
08:30:15AM 7 Jeremy Tigan. I'm with Morris, Nichols in Wilmington on behalf
08:30:19AM 8 of the Plaintiffs. I am joined by my co-counsel today from the
08:30:23AM 9 Cahill Gordan firm. At counsel table I have Gerald Flattmann and
08:30:26AM 10 Andrew Cochran, and our broader team is in the back. Our client
08:30:30AM 11 representatives are here as well, David BanchiK and Alyssa
08:30:35AM 12 Klapper.
08:30:35AM 13 THE COURT: Good morning. And for the defense?
08:30:42AM 14 MS. HANEY: Good morning, Your Honor. Megan Haney from
08:30:46AM 15 Phillips, McLaughlin & Hall in Delaware. And I am joined today
08:30:51AM 16 by Bill Rakoczy, Joe Jaros, Katie Boda, and Adrianne Rose, all
08:31:01AM 17 from Rakoczy, Molino, Mazzochi, Siwik in Chicago. And our
08:31:04AM 18 representative is also here.
08:31:09AM 19 THE COURT: Good morning. So the most important person
08:31:11AM 20 in the room is the court reporter. Can you hear everything okay?
08:31:11AM 21 Is the audio working fine for you?
08:31:11AM 22 THE COURT REPORTER: Yes.
08:31:17AM 23 THE COURT: Please, if you have any problems, don't
08:31:19AM 24 hesitate to speak up, raise your hand, or go over things again to
08:31:23AM 25 make sure we've got a good record.

08:31:26AM And so we have a 10-hour per side civil bench trial and
08:31:36AM we're starting now. We will take a midmorning break, 15 minutes.
08:31:41AM We'll take a lunch break of no more than an hour. We'll take
08:31:45AM another midafternoon break. We'll adjust the closing time to
08:31:49AM what makes sense rather than breaking in the middle of a witness
08:31:53AM or starting a witness for 5 or 10 minutes, have some flexibility.
08:31:56AM Let's see if we can get this wrapped up in 3 days. I believe
08:31:59AM both -- each side wants to present an opening statement.
08:32:03AM Are there any preliminaries before we get to openings?
08:32:09AM MR. JAROS: Yes, Your Honor. We had two objections to
08:32:11AM Plaintiffs' opening exhibits under the pretrial order. We are to
08:32:15AM make those before their statement begins.
08:32:18AM THE COURT: Okay. Great. So we have to deal with that
08:32:21AM substantively. Procedurally or mechanically, for your tech
08:32:27AM people, are there any -- I take it that any exhibits that you're
08:32:30AM presenting are going to show on that screen as well as these
08:32:35AM screens? We'll certainly let you know if there are any issues
08:32:40AM with that.
08:32:41AM Why don't you remind me of the substance of your
08:32:43AM objections to the exhibits. These are demonstrative exhibits;
08:32:47AM correct?
08:32:48AM MR. JAROS: They are. So they are Plaintiffs' opening
08:32:50AM statement demonstratives. And we have not filed these with the
08:32:53AM Court. They were exchanged last evening --
08:32:53AM THE COURT: Right.

MR. JAROS: -- so I can address those.
THE COURT: Please.
MR. JAROS: May I use the podium?
MR. FLATTMANN: Your Honor, if it would be helpful, I can hand a full set of exhibits up to the Court so that --
THE COURT: Please do.
MR. FLATTMANN: -- you can follow along.
THE COURT: It would be very helpful if you have a binder with a set of exhibits or anything like that to hand up. If there's an extra one for my clerk.
MR. FLATTMANN: May I approach?
THE COURT: Please.
MR. FLATTMANN: Is two sufficient, Your Honor, or would you like one for the -- would the court reporter like one as well?
THE COURT: Would the court reporter like one?
THE COURT REPORTER: If you have an extra one.
THE COURT: Is there a set for the defense?
MR. JAROS: May I proceed?
THE COURT: Yes.
MR. JAROS: Your Honor, the first of our objections are with respect to Plaintiffs' PDX Slide 27 and 28. Very simply, those refer to a new publication called Schneider. You can see the name of that article in italics on Slide 27.
In this case, Your Honor, their lead expert identified

08:34:14AM 1 the pH of the stomach as an issue early on. In his opening
08:34:18AM 2 report, he addressed it and cited publications in his reply
08:34:22AM 3 report. Because they got the last word, he addressed it again.
08:34:25AM 4 In deposition, I asked him several questions about that area of
08:34:30AM 5 the case, the pH of the stomach.
08:34:33AM 6 In response to a couple of those questions, he was
08:34:35AM 7 instructed not to answer, With respect to the results of his
08:34:39AM 8 searches for publications with respect to the pH of the stomach.
08:34:45AM 9 He accepted that instruction. And then about a month and a half
08:34:48AM 10 later, we received this publication Schneider in November. So it
08:34:54AM 11 was after the deposition, after the filing of the statements of
08:34:57AM 12 fact with the Court.
08:34:58AM 13 And our position is that's too late. This is well
08:35:01AM 14 within the scope of the subject matter, both his opening and
08:35:04AM 15 reply report. It was addressed in deposition but he was
08:35:07AM 16 instructed not to answer as to what he found. And this
08:35:10AM 17 publication appears to be what he found and was disclosed a month
08:35:15AM 18 and a half later.
08:35:17AM 19 THE COURT: Counsel, why are you instructing your
08:35:19AM 20 witnesses not to respond other than privilege?
08:35:22AM 21 MR. FLATTMANN: My understanding is he was not
08:35:24AM 22 instructed not to respond, Your Honor, When he was asked
08:35:27AM 23 questions about cited literature, which noted that the pH of the
08:35:32AM 24 stomach under the appropriate conditions would be about 4.5. He
08:35:38AM 25 relied on an article, in fact, and this is simply a second

article. He was asked whether there were any other articles. And this is one that he found later after the deposition, after being asked whether or not he was aware of any other cited literature.

THE COURT: What I will do is I'll take it under advisement. If by the break -- and by the way, I'm going to try to not deal with these issues during the flow of the testimony but at the breaks. But if you want to point me to where in the deposition he was instructed not to answer anything like that, if you've got a transcript, it should be in the transcript. And you can show that to me.

MR. JAROS: Yes, Your Honor. We have the transcript ready. We can put it on the screen.

THE COURT: Please.

MR. JAROS: So focusing first on Page 55, Line 17. I asked their expert, Dr. Rudnic. "In preparing your opinions in this case and the Lupin case, did you search for peer reviewed literature stating that a pH of 4.5 is a fasted gastric condition?" The instruction was he could answer yes or no based on privilege. He answered yes. I asked the question, "Did you find any such peer reviewed publications?" And he was then instructed not to answer the question and he followed that instruction.

And then I asked, "To be clear, do you believe you cited in either of your reports in this case a peer reviewed

08:36:54AM 1 publication, whether the author stated a pH 4.5 is a fasted
08:37:00AM 2 gastric condition?" Answer, "Not in this case."
08:37:04AM 3 Our view is, Your Honor, that was his last chance to
08:37:06AM 4 identify this publication, and it didn't come in until a month
08:37:10AM 5 and a half later so it should be excluded.
08:37:12AM 6 THE COURT: After the expert report deadlines and
08:37:16AM 7 rebuttal reports?
08:37:17AM 8 MR. JAROS: Yes. So this is his deposition came in --
08:37:19AM 9 this is September 1. We received this publication in November.
08:37:22AM 10 THE COURT: Okay. That's untimely. What's your
08:37:24AM 11 response?
08:37:24AM 12 MR. FLATTMANN: Your Honor, we can find the
08:37:28AM 13 complimentary part of this transcript, but he did talk about peer
08:37:31AM 14 reviewed literature in this very same deposition, including the
08:37:35AM 15 Kalantzi article.
08:37:36AM 16 THE COURT: Okay. But not the Schneider one?
08:37:38AM 17 MR. FLATTMANN: He did not mention that during his
08:37:39AM 18 deposition. He did find that subsequent to his deposition upon
08:37:43AM 19 being asked these questions about the cited literature in which
08:37:45AM 20 promptly produced to Lupin in this case. Also, it's an article
08:37:51AM 21 that we would potentially intend to use on cross-examination in
08:37:55AM 22 this case for the very same point.
08:37:57AM 23 THE COURT: It does seem like he's already got Kalantzi
08:38:01AM 24 and some other articles may wind up being cumulative and not
08:38:06AM 25 really matter here. Does it matter?

MR. JAROS: It matters, Your Honor, because I did not have the opportunity to cross-examine him on the substance of that publication. It's relatively complex. It includes a number of graphs. Had I had notice even a couple days before the deposition, I could have absorbed it and examined him on it. But he had two shots with his opening and reply report and then could have disclosed it before the deposition if they had found it. And they instructed him not to answer as to what he did find when he went to go look for something.

THE COURT: Why in the world is this privileged? What's the plausible basis for finding an article being privileged?

MR. FLATTMANN: Your Honor, I don't think that this precise question about whether it's cited literature is privileged.

THE COURT: I am going to bar it. I am going to bar it. These kind of games about objections at depositions, I won't stand for that.

MR. FLATTMANN: Your Honor, may we have an opportunity at the break to look at the further context in the deposition?

THE COURT: You may.

MR. FLATTMANN: I believe there's a valid answer to this.

THE COURT: You may but you shouldn't go around trying to block this kind of thing from an expert privilege. It's not

right. And the discovery timeline depends on moving promptly. This is not a good faith basis for privilege. All right. Please proceed.

MR. JAROS: Second objection, Your Honor, is with respect to Plaintiffs' demonstrative Slide 20. On that slide, there are two parts. If you have it in front of you, we can also put it up on the screen. But on the left-hand side, there's a bell curve. On the right-hand side, there's text. We have no problem with the text. That was disclosed fairly. Our problem --

THE COURT: This is Slide 20, you say?

MR. JAROS: Yes, Your Honor. We are not objecting to the text on the right. That was disclosed. On the left, there is a bell curve that represents again the same experts theory as to the distribution.

THE COURT: Is there any evidence that this follows the normal distribution basis for this?

MR. JAROS: There is not. And I am not sure that's a normal distribution. It was called a bell curve in the deposition. So similar concept, Your Honor. This bell curve concept was not disclosed in an opening report, not disclosed in a reply report. It was simply mentioned in the context of deposition when I learned for the first time he had two theories, number one, all the beads are bad. Number two, some of the beads are bad.

08:40:43AM During the deposition, he dropped the all the beads are bad argument and went with the some of the beads are bad. And then we received this a couple days ago, a bell curve representing that some of the beads are bad. So same thing. I did have a chance to examine --

THE COURT: But he mentioned bell curve?

MR. JAROS: He used the word bell curve.

THE COURT: Yeah, this is a close enough approximation if I take it as not to scale necessarily. It just visualizes what he said there. Now, you are entirely entitled to point out how little basis he has for the bell curve. But I will take it for what it is. It's not to scale. It's not to -- it's just like it's visually representing what he said at the deposition.

And since it was mentioned at the deposition and there's no objection here going into the deposition, I am going to allow it. But with an appropriate caveat that I am not supposed to understand that this is the precise scale or shape.

MR. JAROS: I believe I understand, Your Honor. So essentially this is a demonstrative. This is a cartoon.

THE COURT: It's a demonstrative cartoon. It's not like I can measure the height and width precise conclusions from it.

MR. JAROS: With that, Your Honor, as pure demonstrative, we understand, we will withdraw the objection. Thank you.

08:42:05AM THE COURT: Anything else? All right. Plaintiffs
08:42:11AM please begin. Let's start the timer.
08:42:13AM MR. FLATTMANN: Thank you, Your Honor. Gerald
08:42:16AM Flattmann on behalf of the Plaintiffs. Your Honor, this case is
08:42:20AM about the Chang patents that cover the Oracea product. And by
08:42:28AM way of a brief background, Oracea is a once-daily doxycycline
08:42:32AM that's indicated for the treatment of inflammatory lesions,
08:42:39AM papules, and pustules of rosacea in adult patients. Now there's
08:42:39AM no dispute that Lupin's proposed generic product works for that
08:42:44AM indication.
08:42:44AM In fact, the FDA has tentatively approved Lupin's ANDA
08:42:48AM for that very purpose. Now the Oracea patents that are at issue
08:42:56AM in this trial are the Chang patents, specifically the 532 and 740
08:42:59AM patents. And those patents cover Oracea's unique once-daily
08:43:04AM formulation of doxycycline designed to maintain blood levels of
08:43:09AM doxycycline between specific thresholds to achieve the goal of
08:43:12AM providing therapeutic efficacy without antibiotic effects.
08:43:17AM And the way to achieve that goal was to formulate
08:43:22AM Oracea with 30 milligrams of immediate release or IR and 10
08:43:26AM milligrams of delayed release or DR components. And indeed, in
08:43:31AM 2002, Galderma's predecessor, CollaGenex Pharmaceuticals,
08:43:40AM commissioned a study to determine doxycycline's absorption window
08:43:40AM in the body. And it tested different ratios, including 40
08:43:44AM milligrams of immediate release product and it conducted in
08:43:51AM silico simulations that through that testing determined that a 30

08:43:54AM to 10 immediate release to delayed release ratio could best
08:43:59AM achieve the inventor's goal of maintaining those blood levels.
08:44:04AM Now, Your Honor, these are battle-tested patents and
08:44:07AM they've been in litigation time and time again.
08:44:10AM THE COURT: Chang patents are 532 and 740?
08:44:13AM MR. FLATTMANN: Yes, Your Honor. There's been over a
08:44:17AM decade of challenges to the Chang patents and emerged unscathed
08:44:22AM every time. So the Mylan case, the first one on this list, went
08:44:25AM to trial back in July of 2011. And in that trial, Judge Stark
08:44:29AM heard several of the very same arguments that Lupin is going to
08:44:32AM attempt in this trial.
08:44:34AM But Mylan was held to infringe the 532 Chang patent.
08:44:40AM And then the original Lupin patent challenges rose or fell on the
08:44:44AM result of the Mylan case.
08:44:46AM THE COURT: But there's no argument that I'm estopped
08:44:48AM or any kind of estoppel that would apply to Defendants or
08:44:52AM anything else. I'm deciding this anew; correct?
08:44:55AM MR. FLATTMANN: That's correct. You are deciding this
08:44:56AM anew on the facts. But you are going to see analogous patterns
08:45:01AM and fact patterns and --
08:45:03AM THE COURT: That's fine if I'm persuaded, but you're
08:45:06AM not arguing that I'm bound.
08:45:07AM MR. FLATTMANN: That's correct, Your Honor. That's
08:45:09AM correct. And in the Sandoz action, Sandoz walked away from the
08:45:13AM litigation and then pulled its Paragraph IV certification.

08:45:15AM Dr. Reddy's dropped its challenges to the Chang patents, and then
08:45:19AM there were several cases against Amneal.
08:45:21AM THE COURT: Did any of this involve any numbers near 22
08:45:24AM and 18?
08:45:24AM MR. FLATTMANN: Well, yes. For instance, in the most
08:45:28AM recent and relevant one, Amneal reformulated its proposed ANDA
08:45:32AM product with attorney help, as Lupin has done here, and it's
08:45:36AM certified under Paragraph IV. Initiating a litigation that was
08:45:41AM tried by Judge Stark back in 2018 and notwithstanding the product
08:45:45AM superficially different look from formulation 38 milligrams in
08:45:52AM that case of doxycycline pellets and doxycycline delayed release
08:45:58AM layer of 2 milligrams. So even a starker difference in some of
08:46:03AM the components.
08:46:04AM Galderma proved infringement under the doctrine of
08:46:08AM equivalents there. And then there was the Sun case which is also
08:46:11AM similar where Sun superficially attempted to design around the
08:46:15AM asserted claims and Sun had formulated a bilayer tablet that had
08:46:24AM 26.4 milligrams of doxycycline in one layer and 13.6 milligrams
08:46:27AM in the other.
08:46:28AM And Judge Stark found that Sun's product infringed both
08:46:32AM of the patents literally and under the doctrine of equivalents
08:46:36AM despite the superficial differences just like we see here or
08:46:40AM labeling differences I might call them. Where are we now?
08:46:45AM Lupin's ANDA is latest in the long line of design around these
08:46:49AM asserted claims. And it's just the third in a series of attempts

to evade the claims of the Chang patent with a cleverly disguised a functionally viable product. And I submit to you that you will reach the same conclusion as your predecessor in Amneal and Sun case when you hear the evidence and the proofs from Lupin's own ANDA application to the FDA.

THE COURT: Lupin is not a predecessor in interest or otherwise connected to any of those other Defendants?

MR. FLATTMANN: Not to my knowledge. You will hear testimony from Plaintiffs' expert, Dr. Edward Rudnic. Dr. Rudnic is an expert in the invention, design, development, testing, manufacture, and commercialization of drug products, including pharmaceutical formulations. And he's notably the designer and developer of Adderall XR, another well-known and a lot of other commercial drug products.

Your Honor, there's a single issue to be tried in the case and that's whether Lupin infringes asserted claims of the Chang patent. And in this case, it's about infringement. As we know, it's not about invalidity or enforceability.

THE COURT: And you are not really arguing that there's much of a difference between the 532 and 740. These probably stand to fall together.

MR. FLATTMANN: Similar patents. One or two minor differences. For instance, some of the claims require enteric coating and some don't but otherwise they are essentially the same. And notably Lupin's arguments are not going to be anything

08:48:26AM 1 new. They have been heard in many other forms and at least those
08:48:29AM 2 other two cases that I mentioned have been essentially rejected.
08:48:35AM 3 Your Honor, Lupin infringes the Chang patents and the
08:48:38AM 4 evidence will show that their product literally infringes and its
08:48:43AM 5 product is at least equivalent under the doctrine of equivalents
08:48:47AM 6 to a once a day 40 milligrams product consistent with 30
08:48:51AM 7 milligrams immediate release portion and a 10 milligram delayed
08:48:54AM 8 release portion.
08:48:56AM 9 The evidence will show that Lupin's ANDA product is a
08:49:02AM 10 result of Lupin's deliberate tests to copy the Chang patents. In
08:49:07AM 11 fact, Lupin intentionally engineered its product to release about
08:49:11AM 12 30 milligrams or 75 percent immediate release and about 10
08:49:16AM 13 milligrams or 25 percent at a later time following oral
08:49:21AM 14 administration.
08:49:22AM 15 THE COURT: As I understand it, your case rises or
08:49:24AM 16 falls on whether I credit that there is, in fact, a second 8
08:49:28AM 17 milligrams immediate release portion.
08:49:32AM 18 MR. FLATTMANN: Whether or not what they called delayed
08:49:33AM 19 release has another 8 milligrams of immediate release.
08:49:36AM 20 THE COURT: That is the factual issue that I am here to
08:49:39AM 21 decide.
08:49:40AM 22 MR. FLATTMANN: Yes, Your Honor. Yes, Your Honor.
08:49:43AM 23 Whether that 8 milligrams contributes to the immediate release is
08:49:49AM 24 part of it. Lupin will argue that because its label states
08:49:53AM 25 nominally different composition ratio, that its product doesn't

08:49:58AM infringe, the Chang patents and Amneal and Sun, same argument
08:50:03AM that was rejected. So the evidence will show right out of
08:50:07AM Lupin's ANDA that its product release is about 30 milligrams of
08:50:12AM doxycycline immediately from combination of what it calls
08:50:16AM immediate release portion and what it calls its delayed release
08:50:20AM portion. That's really the point here.
08:50:22AM And immediate releases 22 milligrams from so-called
08:50:27AM immediate release portion and about 8 milligrams from its
08:50:29AM so-called delayed release portion, as those terms have been
08:50:33AM construed by this Court. Whatever Lupin labels its delayed
08:50:37AM release portion doesn't change the fact that it functions to
08:50:42AM release.
08:50:42AM THE COURT: I understand this to be a case over the
08:50:44AM facts. I don't understand there to be a real dispute about the
08:50:50AM law or the doctrine of equivalents here. Am I right?
08:50:53AM MR. FLATTMANN: I think you are correct. Nor is there
08:50:56AM a dispute about the construction of the claims as Your Honor and
08:51:00AM your predecessors have construed the claims functionally to
08:51:05AM reflect what actually ends up happening in the body.
08:51:10AM So here is just a mathematical type of representation
08:51:15AM of what we just discussed together. The evidence will show that
08:51:19AM Lupin's ANDA product contains this first pellet which contains
08:51:23AM immediate release doxycycline and second pellet which contains
08:51:27AM both immediate release and delayed release doxycycline. And more
08:51:30AM specifically, it will show that Lupin's second type of pellet or

what they called delayed release portion is actually composed of immediate release and delayed release parts. That's the factual question here.

The immediate release part of the second pellet equals 8 milligrams, and the delayed release equals 10 milligrams. So if you do the math, the sum total of the amount of immediate release in Lupin's product is 30 milligrams and the total amount of delayed release in Lupin's ANDA product is 10 milligrams. So the math doesn't lie ultimately.

THE COURT: So if 8 of the 18 nominally delayed release is functional immediate release, then these numbers add up.

MR. FLATTMANN: Exactly. In any event, our point is that Lupin's product is at least insubstantially different. That's where we get to the doctrine of equivalents if we need to get there.

It's insubstantially different from a 30 milligram immediate release portion and a 10 milligram release portion as claimed. That's because the evidence will show the ANDA product performs substantially the same function in substantially the same way to achieve substantially the same result.

THE COURT: Okay. So for other than immediately following that's already been construed to be about half an hour for the way your theory is that the enteric coat is deliberately thin and weak enough to result in functionally released within half an hour and then the result is obvious in terms of

bioequivalence.

MR. FLATTMANN: That's exactly correct, Your Honor. So notably the FDA has already tentatively approved Lupin's product as bioequivalence and the evidence will show it's not just bioequivalence. It's bioequivalence because it works in substantially the same way as I think Your Honor has followed the line of the argument in the prior slide which also makes it equivalent under the doctrine of equivalents.

So let's walk through the proofs briefly. The evidence will show that Lupin meets the claim element, 30 milligrams immediate release either literally or under the doctrine of equivalents. And that's because upon ingestion, Lupin's ANDA product immediately releases the 22 milligrams of immediate release. And that's in the portion it calls immediate release. They don't dispute that. So we are at least that far along.

And then Lupin's ANDA product immediately releases about 8 milligrams from its so-called delayed release. And how do we know that? First, the evidence will show that what Lupin calls its delayed release portion was intentionally designed with a weak enteric coat.

And second, the evidence will also demonstrate that Lupin's ANDA product with its weakly-designed enteric coat functions to create a 30 milligram immediate release portion and 10 milligram delayed release portion.

And third, the design and function of Lupin's ANDA

08:54:39AM product will demonstrate that it infringes.

08:54:44AM Next slide, please.

08:54:44AM So as mentioned, Dr. Rudnic will testify about the
08:54:48AM design of Lupin's ANDA product. He will explain that Lupin made
08:54:53AM two choices to ensure that its enteric coat prematurely and
08:54:58AM immediately releases. First, it used methylene chloride in its
08:55:03AM manufacturing process. And second, it used a remarkably low
08:55:07AM percent weight gain of the enteric coat stage, very thin coat.
08:55:12AM And he will testify about how those two manufacturing choices
08:55:15AM amounted to a compromised and weak enteric coating that leaks.

08:55:21AM This is from Lupin's own documents that you will see in
08:55:26AM the course of Dr. Rudnic's testimony. Lupin's decision to use
08:55:32AM methylene chloride was deliberate. It's a highly toxic solvent
08:55:36AM that's virtually outlawed in the United States.

08:55:40AM Dr. Rudnic will testify that the properties of
08:55:43AM methylene chloride, which is a non-aqueous solvent layer, that
08:55:51AM alternates in Lupin's product with an aqueous solvent layer, is
08:55:51AM to create a leaky coat.

08:55:54AM He will explain how those are not compatible layering
08:55:57AM processes in manufacturing a drug. He will explain that by
08:56:02AM layering its drug product that way, Lupin compromises not only
08:56:05AM the integrity of each of those deposited layers of methylene
08:56:10AM chloride in the aqueous coat but also the ability of the layers
08:56:13AM to adhere to one another, including at the interface of those
08:56:18AM enteric coats. And Lupin did this to ensure that some of the

doxycycline in what it calls its delayed release portion would leak immediately upon oral administration. And it does leak. Now in contrast, for instance, Oracea uses aqueous solvents only.

Here are cross sectional scanning electron microscope images of Oracea compared to samples from Lupin's late manufactured R&D product that show the difference. As you can see, and Dr. Rudnic will testify, Lupin's samples are stratified at the interface between the layers whereas the Oracea product shows no such defect.

Next slide, please.

Dr. Rudnic will further testify that Lupin selected a percent weight gain at the enteric coat stage that was intentionally weak and caused the subset of the pellets to leak. He will explain that the percent weight gain as a measure of how much of the enteric coat is applied to the entire pellet population is very low.

And as it accounts for the entire pellet population, the enteric coat thickness will not be exactly the same for every pellet. The coatings on each pellet will be dictated by a standard distribution curve, and some pellets may receive a satisfactory coat but a subset of them will not and those will leak immediately.

Dr. Rudnic is going to discuss how Lupin's intentional selection of an 18 percent weight gain at the enteric coat stage ensures that the coat will leak and that some of the delayed

release portion will leak immediately. And simply put, the Lupin formulation, Lupin formulated its ANDA product to track Oracea's formulation very closely, including coating similar sized pellets with the exact same polymer Eudragit. But despite those similarities, it used 18 percent weight gain while Oracea uses 30 percent weight gain.

Dr. Rudnic will explain, based on the data, how Lupin's ANDA shows that an 18 percent weight gain is the thinnest coat that Lupin could possibly apply that would not result in detectible leakage during the *in vitro* dissolution test of pH 1.1, the quality control test. And he will explain that the 1.1 pH testing is not a physiological relevant set but it is a quality control measure that will show whether or not pellets will leak.

He will further explain that in his experience, the range of percent weight gains using the polymer are typically much higher than 18 percent and more in line with Oracea's 30 percent.

Next please.

Now, Lupin's ANDA product functions to release 30 milligrams of immediate release and 10 milligrams of delayed release. The deposition testimony from Lupin's lead formulator and corporate witness, Mr. Avachat, as well as the data in Lupin's ANDA will prove this.

Next, please.

08:59:36AM Notably, all of the data that Dr. Rudnic uses to form his opinions are found within Lupin's ANDA which was submitted to the FDA and confirmed as accurate by Lupin's lead formulator, Mr. Avachat. This is in contrast to what Lupin's experts will rely on here which are post hoc testing results from a batch of product that Lupin manufactured solely for purposes of this litigation and its infringement defense.

And even Lupin's expert, Dr. Buckton, agrees that the batch he relied on was manufactured solely for this litigation. It was never submitted to the FDA. It was never reviewed by the FDA.

Not only is that litigation driven batch and the results of this testing factually questionable, unreliable, and inconsistent with the data submitted to the FDA in Lupin's ANDA, it is clearly legally improper under the controlling Federal Circuit authority, namely the Sunovion case which we've cited.

That litigation inspired batch doesn't control the infringement inquiry. What Lupin has asked the FDA under oath to approve is the subject matter that controls the infringement inquiry in determining whether infringement has occurred.

Next slide, please.

Indeed, Mr. Avachat even testified that quote, "It doesn't matter what we did. What matters is what we filed, namely the ANDA." He further testified that Lupin quote, "Did whatever was required by the regulation to be equivalent in all

09:01:16AM aspects to Oracea." And he and Lupin succeeded.

09:01:21AM Next, please.

09:01:21AM As the Federal Circuit Authority dictates, the relevant
09:01:27AM data for purposes of determining infringement are the ANDA data
09:01:31AM that were actually submitted. Lupin's own data from its ANDA
09:01:35AM reveal how the product actually functions. Specifically, the in
09:01:39AM vitro dissolution data at the more physiologically relevant pH
09:01:44AM 4.5, which is the actual pH upon ingestion as indicated, controls
09:01:49AM and so does the in vivo.

09:01:53AM THE COURT: Mysterious substance that doesn't dissolve
09:01:56AM with a highly acidic 1.1 but somehow dissolves at 4.5?

09:02:01AM MR. FLATTMANN: Well, it's not a mystery because the pH
09:02:03AM 1.1 test is simply a quality control test. It uses the most
09:02:08AM extreme possible situation that could ever occur in the body if
09:02:13AM something contacted gastric juice, as opposed to the pH of the
09:02:19AM stomach, which ranges between 2.4 and 4.5, which it hits when
09:02:23AM you've had 240 mLs of water on a fasting stomach.

09:02:29AM So yes, these are releasing at 4.5, which is the actual
09:02:34AM physiological relevant condition. 1.1 is a control test. It's
09:02:38AM an important test but it's a control test, quality control test.

09:02:43AM So in getting to that on page -- Slide 26, please.

09:02:53AM This is the Kalantzi article that I mentioned during
09:02:55AM argument earlier which Dr. Rudnic relied on in his report. And
09:03:00AM he'll explain that the FDA requires drinking 240 milliliters or
09:03:05AM about 8 ounces of water when conducting bioequivalence studies.

09:03:10AM 1 And that's the same amount of water that Lupin used when
09:03:14AM 2 conducting it's fasting bioequivalence protocol. That's not too
09:03:17AM 3 surprising.
09:03:17AM 4 He'll explain how the scientific community articles
09:03:21AM 5 like Kalantzi measured the pH of the fasting stomach under these
09:03:25AM 6 same FDA mandated conditions and found it to be a pH of
09:03:29AM 7 approximately 4.5 immediately after administration.
09:03:38AM 8 Let's go to 28.
09:03:44AM 9 So this is a slide from Lupin's own bioequivalence
09:03:49AM 10 fasting study. And as you can see on the slide, Lupin's fasted
09:03:55AM 11 state bioequivalence study involved the administration of 240 mLs
09:03:59AM 12 of water to patients that fasted overnight, which necessarily
09:04:02AM 13 would result in a gastric condition of pH 4.5, the relevant data
09:04:07AM 14 here.
09:04:08AM 15 Next slide, please.
09:04:10AM 16 Dr. Rudnic will also explain that in the in vitro
09:04:15AM 17 dissolution test data at 4.5, the data that was actually
09:04:19AM 18 submitted to the FDA, that that data supports the 30 to 10 ratio
09:04:24AM 19 here. And as you can see here, the mean release of Lupin's ANDA
09:04:29AM 20 product in this bioequivalence test submitted to FDA, the lines
09:04:33AM 21 overlap each other when you compare Lupin's bioequivalence PK
09:04:38AM 22 values and blood values to Oracea's data. That's not surprising.
09:04:43AM 23 It's a bioequivalence product and it's been approved.
09:04:45AM 24 And that's the same product that was -- that was
09:04:49AM 25 exposed to pH 4.5. Same product and its bioequivalence matches

09:04:57AM right up. After exposure to pH 4.5, the mean release of Lupin's
09:05:02AM ANDA product is exactly 30 milligrams or 75 percent.
09:05:09AM Next slide, please.
09:05:10AM Dr. Rudnic will also explain that the individual data
09:05:13AM from the in vitro dissolution test at pH 4.5 supports a
09:05:18AM composition ratio of 30 to 10. And as you can see, Lupin's
09:05:24AM individual capsule data show release after exposure to pH 4.5 in
09:05:29AM the stomach whereas Oracea's delayed release portions do not.
09:05:32AM And not leaking.
09:05:38AM The data here also show that Lupin - Lupin's ANDA
09:05:41AM Product release is more than just 22 milligrams immediately.
09:05:45AM That additional release to get to that 75 percent mean number in
09:05:49AM yellow, that additional release of 8 milligrams, it has to come
09:05:53AM from somewhere. And it comes from the so-called delayed release
09:05:57AM portion.
09:05:59AM Dr. Rudnic will explain that Lupin's individual capsule
09:06:05AM data present a continuum of release profiles ranging from 55 to
09:06:08AM 85 percent at that 30-minute mark that we've been looking at.
09:06:12AM And they rely on that very variability, with some capsules
09:06:18AM bursting and some not, to achieve the mean release profile set by
09:06:21AM the profile here.
09:06:23AM THE COURT: I thought that the definition of
09:06:25AM substantially all is within 30 minutes and yet your slide, 1.029,
09:06:31AM has 120 minutes plus another 30 minutes.
09:06:35AM MR. FLATTMANN: Yes. So the timelines for the in vitro

09:06:39AM dissolution test are not directly comparable to what happens in
09:06:44AM the body. So here you're conducting an experiment. You're
09:06:46AM adding different media at different times in the in vitro
09:06:50AM dissolution experiment.
09:06:51AM THE COURT: I got it. I got it. But you're having to
09:06:53AM translate what from in vitro --
09:06:56AM MR. FLATTMANN: Dr. Rudnic is going to do a much better
09:06:59AM job of explaining that than I can.
09:07:01AM THE COURT: Okay.
09:07:02AM MR. FLATTMANN: Slide 31.
09:07:04AM Dr. Rudnic will testify that the results of the fasted
09:07:09AM state bioequivalence studies of Lupin's ANDA product are
09:07:12AM virtually the same as we saw for the results for Oracea. They're
09:07:17AM undisputed 30 milligram immediate release and 10 milligram
09:07:20AM delayed release composition.
09:07:22AM And the fact that the mean plasma concentrations of
09:07:28AM Oracea and Lupin's ANDA product have substantial overlap, you
09:07:31AM know, considering these data together, with all of the other
09:07:34AM evidence that Lupin submitted to the FDA, and it certified to be
09:07:38AM correct and accurate, shows that Lupin's ANDA product has that
09:07:44AM ratio, 30 to 10.
09:07:45AM Let's put it all together in the context of patents.
09:07:50AM Neither Lupin nor its experts dispute that Lupin's ANDA product
09:07:54AM meets all of the elements of the asserted claims, including the
09:07:58AM elements regarding having an immediate release portion and having

09:08:00AM 1 a delayed release portion. The only dispute revolves around the
09:08:04AM 2 claimed ratio.
09:08:07AM 3 Next, please.
09:08:09AM 4 In the Court's construction of the claimed term
09:08:11AM 5 immediate release supports a finding of infringement because the
09:08:15AM 6 term release imparts the functional limitations of claims, and
09:08:20AM 7 the infringement inquiry must account for how the release impacts
09:08:26AM 8 a subject's steady state blood levels in the body.
09:08:29AM 9 So based on all the evidence, Lupin's ANDA product
09:08:32AM 10 releases 30 milligrams of doxycycline immediately to alter the
09:08:37AM 11 subject's steady state blood levels. And that comes, again, from
09:08:42AM 12 a combination of its 22 milligram immediate release portion and
09:08:46AM 13 the 8 milligrams from the delayed release portion on average.
09:08:49AM 14 Next, please.
09:08:49AM 15 As a result of the immediate release of 30 milligrams
09:08:54AM 16 of Lupin's ANDA product, 10 milligrams of doxycycline function to
09:09:01AM 17 release at a time other than immediately following oral
09:09:05AM 18 administration. That's what's left over. It's just the math.
09:09:08AM 19 And that is, again, consistent with the Sun Court and this
09:09:11AM 20 Court's construction of the term delayed release.
09:09:15AM 21 Now, the term -- claimed term portion as conceptualized
09:09:21AM 22 by the Sun Court and adopted by this Court, also supports a
09:09:23AM 23 finding of infringement because the Sun Court elucidated that the
09:09:28AM 24 term portion was a functional limitation, and in particular the
09:09:31AM 25 term was construed to allow for any part of the claimed

composition to contribute an immediate release or delayed release amount depending on the timing of that release.

So contrary to this and the Court's -- and the Sun Court's understanding of the claim terms, Lupin had cited a different case and attempted to state that it is, in fact, analogous to the Reckitt Benckiser case that they brought to your attention, Your Honor.

But in that case, the Court construed the same term portion, they're completely different contexts, have an entirely different meaning. It construed the term "portion" to be structural and singular whereas in Sun, the Court construed portion to be functional and plural, the exact opposite. So as such, the Reckitt case does not control.

Lupin's ANDA product also infringes the Chang patents under the doctrine of equivalents because it's at least insubstantially different from a composition with a 30:10 ratio.

Next, please.

The evidence will show that the design and function of Lupin's ANDA product result in a 30-milligram immediate release 10-milligram delayed release doxycycline product that is equivalent to the asserted claims.

Lupin's ANDA product also infringes the Oracea -- I'm sorry, the Chang method of treatment claims. There are two representative claims being asserted in this case. Claim 19 of the 740, Claim 15 of the 532, and also Claims 20 and 16,

09:11:14AM 1 respectively, which are the dependent claims. And those claims
09:11:17AM 2 are nearly identical to the composition claims that Your Honor
09:11:20AM 3 has reviewed, except that the product is a method for treating
09:11:25AM 4 rosacea in humans in vivo and physiologically relevant context.
09:11:33AM 5 So Lupin's experts, Dr. Buckton and Ms. Gray, will rely
09:11:36AM 6 on a series of flawed opinions and attempt to show
09:11:40AM 7 non-infringement. Dr. Buckton and Ms. Gray will ask the Court to
09:11:46AM 8 focus solely on cherry-picked litigation inspired in vitro
09:11:50AM 9 dissolution data.
09:11:51AM 10 But the evidence will show that Lupin ignores the
09:11:52AM 11 highly probative pH 4.5 data from its own ANDA. And Lupin's
09:11:57AM 12 experts will also largely ignore the in vitro data that Lupin
09:12:02AM 13 relied on to establish bioequivalence and in so doing will fail
09:12:05AM 14 to account for this Court's functional construction.
09:12:09AM 15 Dr. Buckton and Ms. Gray will place undue weight on in
09:12:14AM 16 vitro dissolution data taken from a brand new 6,000-capsule batch
09:12:19AM 17 which was manufactured solely for this litigation and the
09:12:22AM 18 evidence will show that.
09:12:24AM 19 Dr. Rudnic will explain why that batch is not
09:12:26AM 20 representative of Lupin's ANDA product. And why the in vitro
09:12:31AM 21 dissolution data and Lupin's ANDA, which is based on a 230,000
09:12:36AM 22 capsule batch, about 38 times larger batch, is much more
09:12:41AM 23 reliable.
09:12:41AM 24 Dr. Buckton and Ms. Gray will also rely on a so-called
09:12:45AM 25 hotspot phenomenon to explain the release of doxycycline from

09:12:51AM Lupin's delayed release portions in the pH 4.5 test that we're
09:12:55AM relying on. And the evidence will show that this hotspot
09:13:00AM phenomenon is a figment of their imagination. It doesn't exist
09:13:04AM in the literature in any reliable form.
09:13:06AM In conclusion, Your Honor, the evidence will show that
09:13:09AM Lupin infringes each of these asserted claims of the Chang
09:13:12AM patents. Thank you, Your Honor.
09:13:27AM MR. RAKOCZY: Good morning, Your Honor. William
09:13:28AM Rakoczy for the Lupin Defendants. I want to make sure, Your
09:13:32AM Honor, you have the Lupin slides.
09:13:35AM THE COURT: Yes.
09:13:45AM MR. RAKOCZY: May I proceed, Your Honor?
09:13:45AM THE COURT: Please.
09:13:47AM MR. RAKOCZY: I will briefly preview for the Court what
09:13:49AM the evidence will show regarding the asserted patents and the
09:13:53AM Lupin products. Suffice it to say you will hear a very different
09:13:56AM perspective from me than what you just heard. At the end of the
09:14:00AM day, we submit the evidence will show Lupin's product does not
09:14:02AM infringe. In our affirmative case, we will present evidence on
09:14:05AM what the patents teach, the patents claim, and how Lupin's
09:14:08AM product functions.
09:14:10AM In short, Your Honor, the patents teach very precisely
09:14:14AM how to make the claim composition, how to test it, and how to
09:14:18AM describe it. According to those very precise and clear
09:14:21AM teachings, Lupin's product functions as 22 milligrams immediate

09:14:25AM release and 18 milligrams delayed release, which I will call
09:14:31AM 22:18 or the 22:18 IR/DR ratio which is not even close to the
09:14:36AM claimed 30:10 ratio.
09:14:39AM In our rebuttal case, we will show that the so-called
09:14:43AM subset theory is both a contradiction and its been disproven
09:14:47AM definitively. According to that subset theory, Galderma and its
09:14:51AM experts suggest that of the 18 milligrams of Lupin's delayed
09:14:54AM release or DR beads, 8 milligrams will somehow, someway
09:14:59AM immediately and completely release while the remaining 10
09:15:03AM milligrams will work perfectly and continue to delay release as
09:15:07AM intended.
09:15:08AM There's no support for that contradiction, Your Honor,
09:15:11AM no evidence. All of Lupin's DR beads are made the exact same way
09:15:16AM using the same process, using the same ingredients. In fact,
09:15:20AM Lupin uses the same enteric coating that is on Oracea. There is
09:15:24AM no credible evidence that that coating is weak.
09:15:27AM In fact, Lupin used a coating that falls squarely
09:15:30AM within the range allowed in the patents and the testing will show
09:15:35AM that. There's no way to reconcile Galderma's theory, again, that
09:15:39AM somehow 8 milligrams of those DR beads completely and immediately
09:15:43AM fail but 10 milligrams continue to work perfectly.
09:15:47AM But on top of that, we tested that theory. Galderma
09:15:50AM didn't. We tested this pH 4.5 subset theory. We gave Lupin's
09:15:55AM capsules to an independent testing laboratory to see what would
09:16:00AM happen. Galderma conducted no testing in this case on hundreds

of capsules and thousands of beads. We took their theory. We don't agree that this pH 4.5 subset test is a proper test, but we said let's test it and see what happens.

And when we did, the results came back from the independent testing laboratory and it showed no additional immediate release from the DR beads. None. None of those beads failed much less completely and immediately. So there's no support, and we disproved this subset theory.

And with that, Your Honor, all the rest of their case falls, including the blood level theory. They then have a backup theory where they say the blood levels corroborate the ratios because Lupin's ratio is somehow similar to Oracea but that all depends on the subset that somehow there's this subset of 8 milligrams of the DR beads not working.

We disproved that. On top of that, the evidence will show you can't seriously infer composition ratios from looking at blood level.

So Your Honor, we submit at the end of the day, Galderma's infringement theories are not based on science or facts or hard data. They're based on assumption. And their key assumption that somehow Lupin's 22:18 product at pH 1.1 somehow transforms into a 30:10 product at pH 4.5 is not supported, it's wrong, and it's been disproven by our 4.5 pH rebuttal testing.

So we submit we'll be left with one simple truth at the end of this case and that is that using the same test and

09:17:43AM conditions from the prior cases from the Amneal and Sun cases
09:17:47AM that used that pH 1.1 condition to confirm the IR DR ratio there
09:17:53AM will be no general dispute that Lupin's product does not
09:17:56AM infringe.

09:17:56AM And I'd like to emphasize that point again. If we used
09:18:01AM the patent test, the test out of their own patent that was also
09:18:05AM used in the Amneal and Sun litigation, there's no serious dispute
09:18:10AM Lupin's product functions as 22:18. And you don't have to take
09:18:14AM my word for it, Your Honor. We have a slide to prove it. This
09:18:18AM is DDX 1, Slide 3. This is right from Galderma's own statement
09:18:21AM of facts, Paragraph 106.

09:18:23AM The data at pH 1.1, that's the same condition and test
09:18:27AM used in their own patent used in the Amneal and Sun litigation.
09:18:31AM It's also an industry standard test from the FDA, from the US
09:18:37AM Pharmacopeia, which is the standard setting organization for all
09:18:39AM pharmaceuticals in the United States. It's the test they use on
09:18:43AM Oracea.

09:18:44AM At this test, they admit that Lupin's product releases
09:18:47AM approximately 50 percent at 30 minutes and 54 percent at 120
09:18:52AM minutes. And they further admit that's coming from the immediate
09:18:54AM release portion. That equates to a 22 milligram immediate
09:18:59AM release product, 18 milligrams delayed release. Not even close
09:19:03AM to the 30:10.

09:19:05AM With that, Your Honor, I'd like to just highlight the
09:19:08AM few points in our affirmative case, and I'd like to start with

09:19:13AM 1 some discussion about the patent. We didn't hear a whole lot of
09:19:15AM 2 discussion about the patent and the composition ratios. We heard
09:19:20AM 3 a little bit about blood ratios, nothing about this.
09:19:23AM 4 At a very high level here on DDX 1, Slide 5, the
09:19:27AM 5 summary of the invention says, in yellow, it's a pharmaceutical
09:19:31AM 6 composition of doxycycline and it consists of an IR, or immediate
09:19:36AM 7 release component, in purple. I think that's purple. I
09:19:39AM 8 apologize. It's not showing up well. And in blue, a DR
09:19:43AM 9 component.
09:19:43AM 10 And those can be combined in a unit dosage form at a
09:19:50AM 11 preferred ratio. And the most preferred ratio in the patent is
09:19:51AM 12 what you see here, 75 to 25 IR to DR. And that simply means at a
09:19:56AM 13 40-milligram dose, 75 percent is IR, 25 percent is DR. And that
09:20:02AM 14 translates into 30 milligrams IR, 10 milligrams DR, so 75:25 is
09:20:08AM 15 the same as 30:10.
09:20:11AM 16 Now the patents teach the skilled person exactly how to
09:20:16AM 17 make those components to start with the immediate release or IR,
09:20:19AM 18 and we have it in its most simplest form here in example 1 on
09:20:25AM 19 Slide 6. And an easy way to do it is to take a dispersion of
09:20:28AM 20 doxycycline and polymer and spray it on to a sugar seed or bead.
09:20:32AM 21 And that makes what the patent calls an IR bead.
09:20:35AM 22 That IR bead can then be tested, the patent tells the
09:20:39AM 23 skilled person exactly how to did it. It's here in Figure 1 on
09:20:43AM 24 Slide 7, so we will jump to that. This is a figure we didn't
09:20:46AM 25 hear anything about during their opening. They don't want to

09:20:49AM talk about this at all. This is their own test. And I will say,
09:20:53AM Your Honor, it's highly unusual for a patentee to criticize their
09:20:58AM own test and run away from it. Usually they're dying for the
09:21:01AM Defendant to use their test.
09:21:03AM And that's what we did. This is a dissolution test or
09:21:07AM a release profile test. It's pH 1.1 condition measuring at 10,
09:21:14AM 20, 30 minutes,they tested the IR beads and you can see, based on
09:21:17AM that curve, at 10, 20, and 30 minutes, these IR beads release
09:21:22AM virtually all of their drug, as they were intended, designed and
09:21:25AM manufactured.
09:21:28AM The patent also teaches how to make delayed release or
09:21:31AM DR -- this is example 2 on Slide 9. And again, this is a fairly
09:21:35AM simple process where you take the IR bead from the prior example
09:21:40AM and then you spray an enteric or delayed release coating onto it,
09:21:44AM and that's a special coating, Your Honor, that is made to delay
09:21:49AM release in the acidic condition of the stomach and then allow
09:21:54AM release later on in the intestine with a higher pH.
09:21:57AM And here a very simple way to do it is to apply this
09:22:03AM Eudragit L 30 D-55 enteric coating. It's actually the exact same
09:22:09AM coating on Lupin's product and Oracea, the commercial embodiment
09:22:12AM product. So you take that coating, you spray it onto the IR bead
09:22:16AM and now you have a delayed release or DR bead.
09:22:19AM And again, as you can expect, the patent teaches how to
09:22:23AM test for delayed release and it points us to Figure 2. Here we
09:22:28AM have another test Galderma doesn't want to talk about. It's a

09:22:33AM dissolution release profile test, but this is two stages. So
09:22:38AM this starts out at pH 1.1 through 2 hours and then it goes up to
09:22:43AM pH 7.0 in the --
09:22:45AM THE COURT: These are all in vitro tests; right? The
09:22:48AM time is running from the time you put it in a petri dish, not
09:22:52AM from the time --
09:22:52AM MR. RAKOCZY: Correct, Your Honor. These are industry
09:22:54AM standard tests for how you measure both IR and DR. And in the
09:22:59AM first part, the 2 hour at 1.1, that is meant to show you how this
09:23:04AM drug would function upon administration, meaning how would the
09:23:08AM drug dissolve and release from the dosage form upon
09:23:12AM administration. And here in Figure 2, they are testing the DR
09:23:16AM beads. And as you can see, as manufactured and intended, during
09:23:20AM the first 2 hours of pH 1.1 DR beads are releasing no drug
09:23:25AM whatsoever.
09:23:26AM But then when it switches over to the higher pH that
09:23:29AM you would see in the intestine the DR bead is releasing
09:23:34AM substantially all of its drug as you would expect as it was
09:23:36AM manufactured.
09:23:37AM And then finally, we have the combination capsule.
09:23:40AM Here on slide 12 this is example 3. And put simply, you take the
09:23:45AM ratio of the beads that you want and you fill the capsule. The
09:23:50AM most preferred ratio in this example, again, is the 75 percent IR
09:23:54AM or 30 milligrams IR and 25 milligrams DR -- or I'm sorry. 10
09:24:01AM milligrams DR or 25 percent DR and you put those into the

09:24:05AM capsule.

09:24:06AM And we have a test for that as well. The patent points
09:24:09AM us to Figure 3 as we see here on Slide 13 and in Figure 3, that's
09:24:15AM exactly what they do, Your Honor. They take that 40 milligram
09:24:19AM capsule and they put it into the two-stage test and at pH 1.1 at
09:24:24AM the 1-hour and 2-hour time points, you see that this capsule is
09:24:29AM releasing approximately 75 percent immediately or 75 percent IR
09:24:35AM as they put into it and as it was manufactured. And then it's
09:24:39AM releasing the remainder of its drug thereafter in the higher pH
09:24:42AM or the 25 percent DR. So this test is confirming that, in fact,
09:24:48AM upon administration, this capsule is releasing as it was intended
09:24:53AM to, as it was made.

09:24:55AM Now, let's very briefly look at the asserted claims and
09:24:59AM how these concepts are used. I won't belabor this, we've already
09:25:03AM looked at it. But again, Claim 1, an oral pharmaceutical
09:25:09AM composition consisting of in purple 30 milligrams IR and 10
09:25:13AM milligrams DR. And the broadest claims, Your Honor, are about 30
09:25:16AM to 10 and that makes for a variance of a 10 percent at most, so
09:25:22AM our broadest claims are about 30:10. And something I want to
09:25:26AM emphasize here.

09:25:27AM This 30:10 composition ratio, it's obviously a separate
09:25:32AM and independent obligation or requirement of the claims for all
09:25:36AM purposes including infringement. And it was also critical to the
09:25:40AM issuance of these claims. The applicants originally tried for a
09:25:45AM claim to any composition that gives the claim steady state blood

levels. A hard stop. No dose limitation. No component limitation. No ratio limitation. And we see that broad Claim 1 here on Slide 18. This goes all the way back to April of 2003. Claim 1, any composition that hits the blood levels. Full stop. Claim 7 did have the IR/DR ratio, but it was extremely broad, about 99 to 1 to 70:30 so basically covering anything.

They couldn't get these claims. The patent office never allowed these in this form. They were rejected and through a series of amendments, here on Slide 19, we finally see the 30:10 IR/DR claims that we know today. But even these claims were not originally allowed. And that's because the patent examiner found a 23 to 16 IR to DR composition in the prior so she rejected the claims on the ground that 23 to 16 IR to DR was about 30 to 10.

The applicants obviously cried foul and said that can't be the case because 23 to 16 is over 30 percent different from about 30:10. And told the examiner in no case would the skilled person think a variance of 30 percent or greater is accomplished by about. So basically they said, 23:16 not covered by our claims. They disclaimed that. And the only reason I bring it up, Your Honor, is because we believe the evidence will show Lupin's product is 22:18. That is even further away from 30:10 than 23:16. So if we prove, and we believe we will, Lupin is 22:18, that does not infringe 30:10 literally or under any reasonable scope of equivalence.

09:27:40AM I'd like to just touch upon what the evidence will show
09:27:42AM on Lupin's product. I believe much of this should not be in
09:27:46AM serious dispute beginning with paragraph 61 of Galderma's
09:27:51AM statement of facts.
09:27:52AM THE COURT: By the way, that ratio then distinguishes
09:27:54AM your case from the other precedents when you mentioned 26 and
09:27:59AM some other numbers that many of those were not within this as you
09:28:05AM read it safe harbor.
09:28:09AM MR. RAKOCZY: Correct, Your Honor. We're far, far away
09:28:10AM from the prior cases and we're far away even from the the 23:16
09:28:13AM and the prosecution history. Galderma admits, Your Honor, that
09:28:18AM the Lupin product is, in fact, designed and manufactured as a 55
09:28:21AM percent, 45 percent IR to DR product. In short, Lupin takes 55
09:28:27AM percent IR beads and then they set aside 45 percent which they
09:28:35AM then enteric coat to make DR beads. So it's a 55:45 ratio
09:28:39AM product. And that translates into 22 milligrams immediate
09:28:42AM release 18 milligrams DR.
09:28:44AM So 55:45 is 22:18. And that's exactly how the Lupin
09:28:51AM product functions according, again, to industry standard tests,
09:28:56AM the tests from the patent, the tests that they use on Oracea.
09:28:59AM Here on Slide 23, we have a couple things on the left. We have
09:29:04AM the Court's constructions of IR portion and DR portion. And
09:29:09AM again, IR portion being that functional part, any part that
09:29:13AM releases immediately upon administration with no delayed effect.
09:29:17AM And the DR portion being functional that which delays

09:29:21AM release to a time other than immediately following
09:29:26AM administration. On the right what we've done is we have a patent
09:29:29AM Figure 3. We have the dissolution test and we have two sets of
09:29:34AM data. In black, that graph is the 30:10 claimed composition.
09:29:39AM And as we saw earlier, you can see that in pH 1.1 it is releasing
09:29:45AM approximately 75 percent of its drug as expected. That's the way
09:29:49AM it was made, 75:25 IR to DR and it's releasing the rest of the
09:29:54AM drug thereafter.

09:29:56AM In green, we plotted the actual Lupin ANDA exhibit
09:30:00AM batch data. This is the data actually from the ANDA submitted to
09:30:04AM the FDA. This is illustrative, Your Honor. There are dozens of
09:30:10AM tests with this exact same data submitted to the FDA, approved by
09:30:14AM the FDA, it's unchallenged in this case. Galderma has done no
09:30:18AM testing. This data clearly shows that at pH 1.1, the capsule is
09:30:25AM releasing approximately 55 percent of its drug or 22 milligrams
09:30:28AM immediate release, and then releasing the remainder at the higher
09:30:32AM pH. This data is undisputed. No matter how we parse or analyze
09:30:38AM this data, it's all the same.

09:30:40AM Here on Slide 24 this is one example of the actual raw
09:30:44AM numbers that went into the green plot on Slide 23. Slide 24, we
09:30:52AM have the raw numbers. And you can see at 30 minutes, the Lupin
09:30:56AM capsule is releasing 53 percent at 60 minutes, 55 percent at 120
09:31:00AM minutes, 56 percent. So an average of 55 percent release in
09:31:06AM those time points, that is 22 milligrams immediate release. The
09:31:10AM Lupin product is functioning according to all of the tests in the

09:31:14AM 1 ANDA as 22:18.

09:31:17AM 2 You can see the stark contrast between the 30:10
09:31:22AM 3 product and Lupin's ANDA exhibit batches here on Slide 25. In
09:31:30AM 4 purple, we have Oracea, the 30:10 product. Again, you can see
09:31:32AM 5 releasing immediately around 75 percent or 30 milligrams. You
09:31:37AM 6 see the Lupin products blue, red, and green. Those are
09:31:41AM 7 composites of all of the ANDA exhibit batch data. And again,
09:31:45AM 8 releasing starting at 30 minutes and going on anywhere from 50 to
09:31:52AM 9 55 percent. So 30 -- excuse me, 22 milligrams IR, 18 milligrams
09:31:59AM 10 DR.

09:32:00AM 11 And there, Your Honor, we believe the evidence will
09:32:03AM 12 show in the end Lupin's product is designed, made, tested and
09:32:07AM 13 properly labeled as 22:18. I point this out on Slide 26 because
09:32:12AM 14 this is a portion of Lupin's label where it clearly says each
09:32:17AM 15 capsule contains 22 milligrams immediate release pellets and 18
09:32:22AM 16 milligrams delayed release pellets.

09:32:27AM 17 The FDA has approved this label and this ratio. They
09:32:28AM 18 have approved it based on dozens of industry standard tests from
09:32:32AM 19 the ANDA. They have approved it because it is true and accurate.
09:32:37AM 20 Again, those results are unchallenged and the product has been
09:32:41AM 21 approved by the FDA as 22:18 as properly labeled as 22:18.

09:32:47AM 22 THE COURT: Friend on the other side says it's based on
09:32:50AM 23 a cherry picked subset of capsules that were produced.

09:32:55AM 24 MR. RAKOCZY: So, Your Honor, we're talking about two
09:32:56AM 25 different sets. So the data we looked at slide 23 and slide 24,

this is not what he's referring to as cherry picked data. This is data right out of the ANDA submitted to the FDA.

What he's referring to is in rebuttal when they came up with this pH 4.5 theory, we thought to ourselves what's the best way to test whether Lupin's DR beads release in 4.5. We thought, why wouldn't you test them in pH 4.5> we gave them hundreds of capsules and thousands of beads. They tested none. Matter of fact, when we asked their expert at the dep, Why didn't you test anything? He was instructed not to answer for privilege and he refused to answer.

All we know is they've disclosed no testing in this case whatsoever. If they did testing, we don't know about it, they didn't disclose it. But we thought we're going to test this theory. We disagree that this is the proper test to do. So what we did was, because our exhibit batch samples had expired already, and we thought they'd criticize that if we tested those, so we had Lupin make a new smaller batch of ANDA product.

Mr. Avachat, the head of R&D at Lupin, will be here to testify that these 6,000 cap capsules were made the same way as the ANDA product. They are the ANDA product. They were made according to the same processes, they contain the same ingredients and the same amounts. We then took those capsules and gave them to an independent laboratory. They tested them and this is what they saw in pH 4.5: 55.4 percent release from Lupin. That's all from the IR portion. None of the DR beads

failed, much less completely and immediately, as their theory posits. So we believe this completely disproves their pH 4.5 theory.

Putting that aside, Your Honor, I don't want the Court to ignore the fact that using the patent test, that's what we're looking at. The patent test, this is the test from Amneal, the test from Sun. This is actually FDA's test, USP test and Oracea's test. These capsules perform as 22:18 and you will hear no challenge to these results, not a single challenge. They agree with these results.

So we believe that the evidence shows Lupin is 22:18 according to unchallenged dozens of tests submitted to the FDA and even if we want to throw the capsules in pH 4.5 they are showing 55 percent release, immediate release, 22:18. So no matter how you look at it, these don't infringe and, Your Honor, I want to pause and emphasize that again.

If they really thought this pH 4.5 theory had legs, they could have tested it. They could have taken the capsules and the beads and put it in pH 4.5 like we did. We went out of our way to make more capsules to try and give them the benefit of the doubt and test their theory and now they're complaining about that. They tested nothing. We gave them the original ANDA samples, they didn't test them. We gave them samples of this new batch. They didn't test them. We did and we disproved their 4.5 theory.

09:36:30AM So with that, Your Honor, I will end as I began and that is if you use the test from the patent and the test from the prior cases, we submit there's no genuine dispute that Lupin product functions as 22:18 or 22 milligrams immediate release 18 milligrams delayed release. That's not even close to 30:10 literally or under any reasonable scope of equivalence.

09:37:00AM Before I step down, Your Honor, I would like to briefly introduce the live witnesses we will call. The first will be Mr. Makarand Avachat. He is the executive vice president of pharmaceutical R&D, and he oversaw the development of the Lupin product.

09:37:15AM The second is Ms. Vivian Gray, an expert in dissolution testing of pharmaceutical compositions.

09:37:20AM And the third is Dr. Graham Buckton, an expert in formulation development and pharmaceutical composition testing. Thank you, Your Honor.

09:37:28AM THE COURT: Wonderful. Can you give me just a vague estimate of how long you think each of these live witnesses will take?

09:37:37AM MR. RAKOCZY: Mr. Avachat will be approximately 50 minutes to an hour. Ms. Gray will be about 45 minutes, 50 minutes. And then Dr. Buckton will be much longer, 3 to 3 and a half hours.

09:38:01AM THE COURT: All right. Very good. Thank you for that. Plaintiff proceed.

09:38:12AM MR. COCHRAN: Your Honor, Plaintiffs call Dr. Edward
09:38:16AM Rudnic.
09:38:18AM THE COURT: Please. Do you have a rough estimate of
09:38:25AM the length of direct examination here?
09:38:29AM MR. COCHRAN: We will be approximately 2 hours, Your
09:38:29AM Honor.
09:38:49AM MR. RAKOCZY: Under the pretrial order we were supposed
09:38:51AM to raise objections before the examination starts. I have just
09:38:55AM several to some exhibits. I think some have been taken care of
09:38:58AM already.
09:38:59AM THE COURT: Why don't you hand up those books and then
09:39:02AM the Plaintiff will hand out the books for the witness and then I
09:39:05AM can look at the exhibits that we're talking about. It will help
09:39:08AM me while Mr. Rakoczy is discussing them. Review those before we
09:39:18AM swear the witness.
09:39:18AM MR. RAKOCZY: Your Honor, may I approach?
09:39:33AM THE COURT: What exhibits would you like to draw my
09:39:35AM attention to?
09:39:36AM MR. RAKOCZY: Yes, Your Honor, four exhibits.
09:39:39AM THE COURT: We've have already talked about Schneider.
09:39:43AM MR. RAKOCZY: Four slides that were Schneider and those
09:39:46AM are PDX-2.13, 14, 66 and 67. And so unless Your Honor would like
09:39:54AM to hear anything else on Schneider, I can move on to the other
09:39:58AM ones. Four of these slides, PDX-2.53, 55, 61, and 62 again.
09:40:06AM THE COURT: Sorry. Are those slide books that will

help me to see the slide books, too, because he's referring to them by slide? So go over the first one.

MR. RAKOCZY: Schneider was PDX-2, Slide 13, 14, 66, and 67.

THE COURT: Some of these Kalantzi.

MR. RAKOCZY: Yes, we are not objecting to Kalantzi.

THE COURT: To the extent these are substantiated by Kalantzi that's fine. What was the next?

MR. RAKOCZY: The next set were more of the bell curve, Your Honor.

THE COURT: Which again, I'm okay allowing as a demonstrative cartoon now understood not to scale.

MR. RAKOCZY: My issue now, Your Honor, is it changed. It started -- if you look at PDX-2, Slide 53, they now have started to add numbers to it on both.

THE COURT: I don't see a number on 53.

MR. RAKOCZY: I'm sorry, Your Honor. Slide 55 and 56. They're now adding numbers and a cross hatch graph.

THE COURT: This is just -- appears to be speculation.

MR. RAKOCZY: We submit it is. It's one thing in our view to mention a bell curve, it's another to attempt to start to make -- what appears to be implying actual distributions here.

MR. COCHRAN: Your Honor, these are the averages. The Lupin 18 percent Oracea --

THE COURT: I think the witness is testifying to this.

I think it's more a question of whether the witness has any foundation or whether it's speculation as to whether these numbers belong at these peaks.

MR. RAKOCZY: Well, he can -- Your Honor, the 18 percent and the 30 percent are the average coating weights on the products, but what he's done is he's put that at the top and then drawn extremely wide bell curves of distribution of -- between weakly coated and more robustly coated and then put the cross hatching --

THE COURT: But then he's suggested that the distributions barely overlap in the middle. And so I'm not going to treat the overlap that's for which it doesn't seem like there's a basis. Like, yes, these are average coating weights, but as to how that plays out, how far apart the curves are, etc., you know, there's a foundation -- there's going to be a foundation issue.

MR. COCHRAN: There's a -- Dr. Rudnic, I'll be asking him about these curves. These are exemplary curves and he'll be testifying.

THE COURT: Okay. We're going to use this as a demonstrative and talk about the foundation for it.

What else?

MR. RAKOCZY: My last two objections, Your Honor, are just to, for the record, I want to renew them so that they are not waived. And that is Slide 68 and 69 are the subject of our

09:43:28AM MIL or motion in limine Number 1. And I just want to put on the
09:43:30AM record that we renew our motion in limine as to use of any time
09:43:36AM points, such as 150 minutes, 180 minutes and 240 minutes to prove
09:43:41AM immediate release.

09:43:43AM THE COURT: I think they're not dispositive. It may be
09:43:48AM that there's an inference to be drawn, that inference may well be
09:43:51AM weak, but the Court is mindful of the, you know, roughly,
09:43:53AM 30-minute time for immediate release as the dispositive one as I
09:43:59AM have construed the claim. So I don't think that makes it
09:44:01AM inadmissible, but it certainly goes to the weight.

09:44:04AM MR. RAKOCZY: Understood, Your Honor. We just wanted
09:44:05AM to preserve that objection.

09:44:06AM And then the last objection I had was Slide 73. And
09:44:10AM this is just to renew our Daubert objection to testimony, any
09:44:16AM testimony attempting to infer composition ratios from mean plasma
09:44:24AM concentration data, which was the subject of our Daubert. Again,
09:44:26AM I understand Your Honor denied it, but I just want to renew it
09:44:30AM for the record.

09:44:31AM THE COURT: Look, the ultimate test is whether they
09:44:33AM infringe the terms of the patent. Mr. Flattmann's opening
09:44:39AM statement went hard on things and, you know, the FDA and blood
09:44:44AM levels and the like. That's not the governing legal test as to
09:44:50AM whether they want to draw inferences from them. You know,
09:44:53AM there's plenty of room to dispute how strong an inference I
09:44:58AM should draw from them. I don't think it makes it inadmissible.

09:45:01AM MR. RAKOCZY: Understood, Your Honor. Thank you.

09:45:02AM THE COURT: All right. Please go ahead and swear the witness.

09:45:05AM EDWARD RUDNIC, called and sworn.

09:45:24AM THE COURT: Good morning, Mr. Rudnic. She's the most important person in the room. If she can't hear you, it doesn't wind up on the record. So please be sure not shaking your head or nodding your head. If at any time you can't hear anybody, let us know.

09:45:39AM If you want to take a break, we're going to take a midmorning break sometime in the next hour, bathroom break, anything else, that's absolutely fine. And I will let people in the courtroom, by the way, I'm not bothered if some of you need to slip out quietly and go to the restroom and come back. Just do it unobtrusively.

09:45:59AM But we'll take a break and let us know if there's a time that either of you need to take it or it's a very logical time to take it. Counsel may figure out a time before transitioning to some other topic that makes sense to take a break in half an hour or 45 minutes or whatever. And I will defer to you and let you go.

09:46:19AM MR. COCHRAN: Thank you, Your Honor.

09:46:21AM THE WITNESS: Before we start, can I try the microphone?

09:46:31AM THE COURT: Yes.

09:46:31AM DIRECT EXAMINATION

09:46:31AM BY MR. COCHRAN:

09:46:33AM Q. Good morning, Dr. Rudnic. Just for the record, please state
09:46:35AM your full name.

09:46:36AM A. Edward Michael Rudnic.

09:46:39AM Q. How to you spell your last name?

09:46:43AM A. R-U-D-N-I-C.

09:46:43AM Q. I understand you will be using a demonstrative to assist you
09:46:46AM in your testimony today; is that correct?

09:46:48AM A. Yes, sir.

09:46:48AM Q. Who prepared those?

09:46:49AM A. I did with assistance of counsel.

09:46:53AM Q. Where are you currently employed, Dr. Rudnic?

09:46:55AM A. I am the chief operating officer and head of research and
09:46:58AM development for Maxwell Biosciences in Austin, Texas.

09:47:05AM Q. What does Maxwell Biosciences do as a business?

09:47:08AM A. We discover and develop new chemical entities for
09:47:16AM antiinfectives. Mostly antibacterials and antifungals at the
09:47:20AM moment.

09:47:20AM Q. Can you please describe your educational background,
09:47:23AM starting with your undergraduate degree.

09:47:26AM A. I have a Bachelor's of science in pharmacy, which allowed me
09:47:29AM to become a registered pharmacist. I went on for a Master's of
09:47:34AM Science in pharmaceutics. And then a Ph.D. in pharmaceutical
09:47:39AM sciences all from the University of Rhode Island.

09:47:42AM Q. What year did you earn your PH.D?
09:47:43AM A. 1982.
09:47:46AM Q. Can you briefly describe your professional experience.
09:47:48AM A. I started with about one-year onsite research internship at
09:47:54AM Merck in Pennsylvania, while I was in graduate school, creating
09:47:58AM research information for my Master's degree. I then, also, spent
09:48:06AM about 8 months onsite at Pfizer in New York doing additional
09:48:11AM research for my graduate degree.
09:48:14AM Following graduation, my first full-time job was at
09:48:17AM Bristol Myers Squibb where I was in charge of a controlled
09:48:21AM release development laboratory. So modified release dosage forms
09:48:26AM their evaluation, testing, and formulation. I then moved from
09:48:32AM that position to be manager of pharmaceutical process development
09:48:41AM at Merck where my job was to manage the scale of all non-sterile
09:48:48AM dosage forms at the company.
09:48:49AM So all tablets, capsules, ointments, creams,
09:48:53AM suspensions, liquids, powders, stuff like that. Big job. And we
09:48:56AM developed a lot of products at -- while I was there. I played a
09:49:03AM major role in the development and ANDA filing of Claritin, a very
09:49:08AM successful cold and allergy product that's still on the market
09:49:13AM today. Cumulative sales of that product and product line are
09:49:17AM about $40 billion. So big deal.
09:49:21AM I left that position when we had acquired Key
09:49:31AM Pharmaceuticals in Miami, Florida. I was promoted to director of
09:49:34AM formulation development. I went down to run the formulation and

development and scale-up activities down at what became known as Schering, Miami. I was responsible for those things for about 5 years. Left that position to become vice president and head of research for a small company called Pharmavene. And while I was at Pharmavene, I had invented three drug products; Adderall XR, Carbatrol and Equetro.

Those three products together caught the attention of Shire Pharmaceuticals, a British company who then acquired Pharmavene. I then became the head of US research for Shire. Preclinical research all the way through initial clinical studies, all the way through pivotal clinical study and post marketing studies. And that position I had all of the formulation development scale up and manufacturing at a pilot scale reporting to me. I had medical clinical regulatory affairs and basic research all reporting to me.

I had that position for about 3 years. When the chairman of Shire had convinced me to leave Shire, to start a new antibiotic company as the CEO, which they were funding through his venture fund. I started that company as Employee 1 and within 3 years took it public on the NASDAQ. It was the first S1 filing to go public post -- and was actually kind of an interesting ride on that IPO.

But it was an antibiotics company. I invented two antibiotics products there that ultimately won FDA approval. And I had left that company after 9 years as CEO and put it in the

09:51:48AM hands of a marketing and sales team. I went on to do some
09:51:52AM venture work and hedge fund work. Didn't particularly like that
09:51:56AM much. I liked operational roles better. I came back to be the
09:52:00AM chief operating officer, and ultimately CEO, of a publicly traded
09:52:07AM Australian company called QRx, it's a pain company. They were in
09:52:11AM under duress and I took over the company as CEO at the request of
09:52:15AM their board to see if I could save it with the FDA. I couldn't.
09:52:19AM So I left QRx and became the CEO of a pharmaceutical
09:52:26AM technology company in Austin, Texas called DisperSol
09:52:31AM Technologies. This is a company with fabulous unique technology
09:52:36AM for the improvement of dissolution and absorption of hard to
09:52:41AM absorb drugs. My role as CEO, and all over research company, was
09:52:48AM to get the technology validated.
09:52:52AM I was able to take two compounds, take it through Phase
09:52:57AM 1, Phase 2, and ultimately into Phase 3 clinical trials, where
09:53:01AM they are today. The company has decided to out -license those
09:53:06AM compounds and turn the company into more of a services model.
09:53:13AM And I'm not much on sales and marketing. I decided to stick with
09:53:20AM research and operations, so I moved over to Maxwell Biosciences
09:53:26AM almost 2 years ago.
09:53:27AM Q. Are you still doing research?
09:53:29AM A. Every day.
09:53:31AM Q. Do you also hold any academic positions?
09:53:34AM A. I am the assistant associate -- no. Associate Professor of
09:53:42AM Pharmaceutics at the University of Maryland and associate

professor of Pharmaceutics at the University of Rhode Island.

Q. Have you published any scientific literature?

A. I have over 20 publications in peer review journals. And seven book chapters in standard reference textbooks, such as Remingtons and Modern Pharmaceutics.

Q. What is the general subject matter of those publications?

A. Starts with oral solid dosage forms, coating tablets, capsules, pellets, drug delivery, novel drug delivery systems, quality control scale up, it's polymer science. And quality control.

Q. When you say "polymer science," what do you mean?

A. Early in my career I did a fair amount of research on the impact of molecular structure variations of polymers and how that affected those polymers' ability to either enhance or suppress drug delivery in the body.

Q. Are you involved in any professional organizations related to pharmaceuticals?

A. Yes, I am a charter member of the American Association of Pharmaceutical Scientists. I have been very active in that organization since its founding. And I've been involved in various discussion groups, working groups and invited to lecture at the Arden House Conference, which is very prestigious thing.

I have also been an invited lecturer at various APS events, such as the Land O Lakes conferences and the national meetings.

09:55:34AM Q. Any other professional organizations?
09:55:37AM A. I am a fellow of the United States Pharmacopeial Convention
09:55:41AM and I am also the past vice chair of biotechnology for the tech
09:55:48AM counsel of Maryland. And the past chairman or chairman emeritus
09:55:52AM of the tech counsel of Maryland.
09:55:55AM Q. What does it mean to be a fellow of the USP?
09:55:58AM A. It's a very prestigious thing. I wasn't aware of how
09:56:03AM difficult it was to get it at the time, but they choose
09:56:06AM relatively young researchers that have done a lot of very
09:56:10AM important work on drug standards or material specifications. And
09:56:17AM my work on polymers caught their attention and I was awarded a
09:56:21AM fellowship.
09:56:21AM Q. Thank you. And what does it mean to be the chairman of the
09:56:26AM Tech Council of Maryland?
09:56:27AM A. This is actually a very prestigious role. So the Tech
09:56:32AM Council of Maryland is the largest traded association in that
09:56:34AM state. It represents about 400,000 jobs in a state of 8 million
09:56:38AM people. And it represents high technology companies, so think
09:56:45AM Lockheed Martin, NASA and IBM and biotech companies. So think
09:56:54AM AstraZeneca, Amgen and hundreds of small biotech companies and I
09:56:57AM was elected by peer CEOs.
09:57:02AM Q. Are you the name inventor on any patents?
09:57:06AM A. Yes, I am the inventor or coinventor on 58 issued US
09:57:11AM patents. I was recently informed that the patent office has
09:57:16AM granted claims on number 59, so that should issue already -- paid

09:57:21AM 1 the issue fee, so should issue soon. So 58 going on 59 and there
09:57:27AM 2 are 12 pending along with about 250 international patents and
09:57:33AM 3 publications that are related to those 58.
09:57:36AM 4 Q. Thank you. Of the drugs you have worked on over your
09:57:39AM 5 career, how many have you commercialized?
09:57:42AM 6 A. Over 80 products.
09:57:46AM 7 Q. Collectively, how much in cumulative sales of those 80
09:57:52AM 8 commercialized products earned?
09:57:53AM 9 A. Last time I checked was well over $100 billion.
09:57:57AM 10 Q. And of those over 80 commercialized products, how many were
09:58:01AM 11 you the lead inventor on?
09:58:03AM 12 A. Seven.
09:58:03AM 13 Q. Can you name them?
09:58:13AM 14 A. Adderall XR, Carbatrol, Equetro, UNI-DUR, Moxatag, GoodNight
09:58:13AM 15 and GI Comfort.
09:58:15AM 16 Q. How common is for someone to be the lead inventor on seven
09:58:19AM 17 commercialized drug products?
09:58:20AM 18 A. It's not common. I have worked with a lot of incredibly
09:58:25AM 19 smart and dedicated people that have worked their entire careers
09:58:29AM 20 and never had a drug product get on the market.
09:58:32AM 21 THE COURT: How much of those involved extended
09:58:33AM 22 release. I'm guessing --
09:58:35AM 23 THE WITNESS: All of them, Your Honor. All of them.
09:58:35AM 24 BY MR. COCHRAN:
09:58:39AM 25 Q. So what challenges are there in commercializing drug

09:58:43AM products containing delayed release components?
09:58:46AM A. Quite a bit. As I mentioned, it's not uncommon to have
09:58:50AM people work in this industry and never have a drug product get to
09:58:55AM the market, because of toxicology issues or other things that
09:58:58AM happened during the normal course of development. But when you
09:59:00AM modify the release of compounds, more things can happen.
09:59:07AM I've seen extended release, modified release dosage
09:59:11AM forms cause toxicity that you didn't see before. I have seen
09:59:16AM therapeutic failure that you didn't see before with an immediate
09:59:19AM release. So added risk starts to come when you start to do those
09:59:24AM things.
09:59:25AM Q. Dr. Rudnic, do you have a witness book containing documents
09:59:29AM that you intend to use today?
09:59:31AM A. Yes.
09:59:32AM Q. Let's turn to PTX-214. It's Tab Number 1.
09:59:38AM Do you recognize this document?
09:59:40AM A. Yes.
09:59:41AM Q. What is it?
09:59:44AM A. It is a reasonably recent version of my CV.
09:59:50AM Q. Does your CV fairly and accurately summarize your education,
09:59:54AM employment, publications and professional accomplishments?
09:59:58AM A. Yes.
09:59:59AM MR. COCHRAN: Your Honor, Plaintiffs would like to
10:00:01AM offer PTX-214 into evidence.
10:00:04AM THE COURT: Any objection?

10:00:05AM MR. RAKOCZY: No objection.

10:00:07AM THE COURT: So entered.

10:00:07AM (Exhibit Number PTX-214 was admitted.)

10:00:10AM MR. COCHRAN: We would also like to offer Dr. Rudnic as ane expert in invention, design, development, testing, 10:00:13AM manufacturing and commercialization of drug products, including 10:00:14AM pharmaceutical formulation.

10:00:18AM THE COURT: Any objection or request for voir dire?

10:00:20AM MR. RAKOCZY: Subject to the grounds stated in our 10:00:23AM Daubert motion, which we understand Your Honor denied, we have 10:00:29AM no objection.

10:00:29AM THE COURT: You may proceed.

10:00:34AM BY MR. COCHRAN:

10:00:34AM Q. Can you provide a high-level summary of the issues in this 10:00:35AM case?

10:00:39AM A. Yes. My opinions can be pretty much summarized into two 10:00:39AM statements. One is that the asserted patent claims cover a 10:00:47AM modified release formulation of doxycycline, which contains a 10:00:51AM 30-milligram immediate release portion and a10-milligram delayed 10:00:55AM release portion. And Lupin's non-infringement defense rises and 10:00:58AM falls with the amount of immediate release and delayed release 10:01:04AM doxycycline it alleges in its formulation.

10:01:07AM Q. Can you walk us through some of the concepts that you plan 10:01:10AM to speak about today?

10:01:13AM A. Sure. So first I'm going to talk about the scientific 10:01:15AM

10:01:20AM background and there's -- it's important to talk about a variety
10:01:23AM of things. The most important things to talk about in vitro
10:01:27AM dissolution testing and its limitations. There are limitations
10:01:32AM to in vitro testing.

10:01:34AM So every test, every set of data tells you something,
10:01:38AM but it's important to understand what it doesn't tell you. It's
10:01:41AM important to understand what its limitations are and I am going
10:01:43AM to talk about that.

10:01:45AM In addition, doxycycline has a very pronounced
10:01:50AM absorption window. It's been well documented over the last 30
10:01:53AM years and it's been well documented in the Oracea NDA, so this is
10:01:58AM something that's been discussed at virtually every case for
10:02:01AM doxycycline since 2011.

10:02:05AM I'm going to talk about the product overview, what
10:02:08AM Oracea and Lupin labels tell us about each product. And again,
10:02:13AM as Mr. Flattmann outlined at the beginning, the only real dispute
10:02:18AM is the quantities of IR and DR. In terms of infringement, what
10:02:24AM I'm going to talk about is Lupin's design and how it functions,
10:02:31AM renders it to be a 30-milligram IR and 10-milligram DR and as a
10:02:36AM result, it infringes the asserted claims.

10:02:39AM Q. Thank you, Dr. Rudnic.

10:02:40AM Let's talk about the scientific background a bit,
10:02:43AM starting with in vitro dissolution. How does the USP website
10:02:48AM define in vitro dissolution testing?

10:02:50AM A. They say that a dissolution experiment evaluates the rate

and extent that a compound forms a solution under carefully controlled conditions.

Q. Thank you. Can you please turn to PTX-143 in your witness book. This is Tab 2.

A. Yes.

Q. Do you recognize this document?

A. Yes.

Q. What is it?

A. It is an excerpt from the USP website talking about dissolution test.

Q. Did you consider PTX-143 in forming your opinions in this case?

A. Yes.

THE COURT: Remind me what USP is.

THE WITNESS: United States Pharmacopeia for drugs and materials used in pharmaceutical products.

MR. COCHRAN: Plaintiffs would like to offer PTX-143 into evidence.

THE COURT: Any objection?

MR. RAKOCZY: No objection.

THE COURT: So admitted.

(Exhibit Number PTX-143 was admitted.)

BY MR. COCHRAN:

Q. Dr. Rudnic, what information is *in vitro* dissolution testing designed to provide?

10:03:49AM A. Well, it is used to assess the lot-to-lot quality of drug products. It guides development of new formulation and ensures continuing product quality and performance after certain changes.

Q. Can you please turn to PTX-163. This is tab 3.

A. Yes.

Q. Do you recognize this document?

A. Yes, this is the FDA guidance for industry on dissolution testing of immediate release solid oral dosage forms.

Q. And is this the FDA guidance you're referencing on your slide?

A. Yes.

MR. COCHRAN: Your Honor, I would like to offer PTX-163 into evidence.

THE COURT: Any objection?

MR. RAKOCZY: No objection, Your Honor.

THE COURT: Admitted.

(Exhibit Number PTX-163 was admitted.)

BY MR. COCHRAN:

Q. Dr. Rudnic, what are the limitations of *in vitro* dissolution testing?

A. It's important, especially for the purpose of this case to note that their primary purpose is quality control. The Lupin experts continually try to point to the fact that certain times of release in dissolution testing are one-to-one relationships what happens in the body. That is not true. In fact, the FDA

10:05:12AM and the USP are very clear their discussions about their test
10:05:21AM that that is not the case.
10:05:23AM So it's important to understand that what these in
10:05:27AM vitro release tests are meant to be, they're quality control
10:05:31AM tests. I've said this consistently throughout this case. Now
10:05:35AM failure of these tests is a concern. But one to one being able
10:05:44AM to tell exactly what is released in the body based on these tests
10:05:49AM is not true. The apparatus design is not the same as what
10:05:53AM happens in the human body. The human stomach is, roughly, got
10:05:59AM about 250 MLs of gastric fluid in it.
10:06:05AM Q. What do you mean by MLs?
10:06:07AM THE COURT: Quarter of a liter. I understood. Go on.
10:06:09AM THE WITNESS: Yes, sir.
10:06:10AM So the testing vessel holds about 900 MLs, almost one
10:06:18AM liter. So in addition you have a paddle that stirs very slowly
10:06:26AM at one revolution per minute, roughly. And the agitation in the
10:06:31AM stomach is a whole lot different.
10:06:34AM The other thing is that the media for a lot of these pH
10:06:39AM 1.1 that doesn't exist in your stomach, it is meant to be the
10:06:44AM fluid that your stomach actually exudes, but the pH of the
10:06:49AM stomach, it if it were 1.1 you wouldn't have much of a stomach
10:06:53AM left after a while, you would have a lot of holes in it. So our
10:06:57AM Mother Nature has given us buffers and salts and other things
10:07:01AM that help protect the lining of our stomach from that gastric
10:07:05AM fluid, and such, the pH is higher. Typically about 2.2 at the

lowest to about 5 at the highest.

And I've been very consistent saying that if you want to pick a good average pH for the stomach, 3 is the number. But what we're going to show is that the pH of time of drug administration is a bit higher.

BY MR. COCHRAN:

Q. So in your opinion, Dr. Rudnic, can a person of ordinary skill in the art rely exclusively on *in vitro* dissolution testing?

A. No. In fact, if you could the FDA wouldn't require bioequivalence testing.

Q. Let's turn to PTX-137 of your witness book. This is tab 4.

A. Yes, I got it.

Q. What is this document?

A. This is also from the FDA website on dissolution methods and disclaimer.

Q. And did you rely on PTX-137 in forming your opinions in this case?

A. Yes.

MR. COCHRAN: Your Honor, Plaintiffs would like to offer PTX-137.

THE COURT: Any objection?

MR. RAKOCZY: No objection, Your Honor.

THE COURT: Admitted.

(Exhibit Number PTX-137 was admitted.)

10:08:13AM BY MR. COCHRAN:
10:08:14AM Q. Let's also turn to PTX-145. That's tab 5.
10:08:14AM A. Got it.
10:08:21AM Q. What is this document?
10:08:21AM A. This is a paper by Deanna Mudie, Gordon Amidon, and Greg
10:08:29AM Amidon from the University of Michigan, they're probably happy
10:08:34AM this morning.
10:08:36AM Gordan Amidon is one of the best experts in terms of
10:08:40AM dissolution testing and what it means for evaluation in vivo and
10:08:44AM in this paper they outline limitations to in vitro testing and
10:08:52AM correlation to in vivo activity and performance.
10:08:56AM Q. Did you rely on this Mudie article in your testimony?
10:08:59AM A. Yes.
10:09:01AM Q. Did you consider --
10:09:03AM MR. COCHRAN: Your Honor, Plaintiffs would like to
10:09:04AM offer PTX-145 into evidence.
10:09:07AM THE COURT: Any objection?
10:09:08AM MR. RAKOCZY: No objection, Your Honor.
10:09:09AM THE COURT: Admitted.
10:09:09AM (Exhibit Number PTX-145 was admitted.)
10:09:09AM BY MR. COCHRAN:
10:09:12AM Q. Now Dr. Rudnic, is there an industry standard for basic drug
10:09:18AM release or testing basic drug release?
10:09:22AM A. Well, I would say no one standard, but probably the majority
10:09:29AM of immediate release dosage forms are tested at pH 1.1. As I

10:09:34AM pointed out, this is kind of the worst case pH that you can have.
10:09:40AM This is the same pH of the acid that your stomach excretes but
10:09:45AM not the pH that is in the stomach in general. So for IR
10:09:50AM products, this is probably the majority of testing.
10:09:55AM Q. Would you consider pH 1.1 a bio relevant pH?
10:09:59AM A. No, because it doesn't exist in the stomach as a general pH.
10:10:05AM It is meant as a QC test. The other thing is it typically runs
10:10:10AM for at least 2 hours. GI transit is certainly about an hour or
10:10:14AM less.
10:10:15AM Q. Why would Lupin use pH 1. --
10:10:18AM THE COURT: GI transits over what part of the
10:10:22AM gastrointestinal tract are you talking about --
10:10:22AM THE WITNESS: Sorry, Your Honor.
10:10:22AM THE COURT: From where to -
10:10:26AM THE WITNESS: Gastric. So you start with the stomach
10:10:29AM and the transit is somewhat less than an hour to go through the
10:10:34AM pylorus into the intestinal tract.
10:10:37AM THE COURT: From entering the stomach to --
10:10:39AM THE WITNESS: From swallowing.
10:10:39AM THE COURT: From swallowing.
10:10:40AM THE WITNESS: From the time it leaves your stomach to
10:10:42AM go into the small intestine.
10:10:47AM THE COURT: Okay. The duodenum?
10:10:47AM THE WITNESS: Duodenum, yes.
10:10:49AM THE COURT: Got it. Mouth, duodenum, one hour?

10:10:51AM THE WITNESS: Correct.

10:10:53AM Now you then go into the duodenum and then at some
10:10:58AM point, and this varies considerably depending on a lot of
10:11:03AM factors, you then go into the duodenum and then ilium and
10:11:09AM ultimately the colon and then it's out.

10:11:09AM BY MR. COCHRAN:

10:11:13AM Q. So Dr. Rudnic, why would Lupin use pH 1.1 in their in vitro
10:11:20AM dissolution testing?

10:11:21AM A. This is pretty much what the FDA asks you to do for
10:11:23AM immediate release dosage forms. Also when they do a modified
10:11:30AM release dosage form they want you to do a mixed test where you
10:11:35AM start with pH 1.1, again, a worst case for 2 hours. And then
10:11:40AM they recommend that you then test for 4.5 -- at pH 4.5 and all
10:11:47AM the way up to about pH 7.5.

10:11:50AM Q. Why would they do that?

10:11:51AM A. Because they recognize that a lot of controlled release
10:11:55AM dosage forms have a full day of drug in them and so they are
10:12:03AM trying to look for dose dumping, which is a concern. So you
10:12:07AM don't want to have a big spike of a full day's dose of drug. So
10:12:11AM that's the purpose for testing at pH 1.1 for 2 hours, make sure
10:12:15AM you don't have that dose dumping. And that whatever controlling
10:12:20AM mechanism you have is robust enough to get through the stomach.

10:12:25AM In addition, you then -- the FDA then asks you to test
10:12:30AM at pHs of 4.5 all the way to 7.5. This is all through FDA
10:12:37AM guidances that have been around for over 20 years.

10:12:42AM Q. Dr. Rudnic, if you wanted to test a product at a pH of the
10:12:46AM stomach, what pH values might you use?
10:12:51AM A. I think you take a look at pHs at the extremes, probably
10:12:55AM start at 1.1 and look at the other extreme 4.5, 5. And some pH
10:13:05AM in between, but certainly those extremes.
10:13:08AM Q. Let's turn to PTX-149 in your witness book. This is tab 6.
10:13:08AM A. Yes.
10:13:14AM Q. What is this document?
10:13:15AM A. This is a paper by Lida Kalantzi. She was a researcher in
10:13:22AM Christos Reppas' group in Greece.
10:13:23AM Q. Did you consider PTX-149 in forming your opinions in this
10:13:28AM case?
10:13:28AM A. Yes, I did.
10:13:29AM MR. COCHRAN: Your Honor, Plaintiffs would like to
10:13:30AM offer PTX-149 into evidence.
10:13:32AM THE COURT: As I understand it, Kalantzi is agreed
10:13:35AM upon; correct? And Schneider, that was the subject of the
10:13:37AM objection; right?
10:13:38AM MR. RAKOCZY: Correct, Your Honor. No objection to
10:13:40AM Kalantzi.
10:13:41AM THE COURT: Admitted.
10:13:41AM (Exhibit Number PTX-149 was admitted.)
10:13:41AM BY MR. COCHRAN:
10:13:44AM Q. Dr. Rudnic, what does the Kalantzi article tell you?
10:13:48AM A. First let's talk about what Kalantzi did. FDA requires that

10:13:55AM when you test a drug product that you take 240 ML of water and
10:14:01AM you take whatever test product you are going to test with that.
10:14:06AM And so Kalantzi tested what actually would be the pH in the
10:14:10AM stomach given the FDA testing parameters.
10:14:15AM And so here, what they showed -- and unfortunately a
10:14:19AM bunch of unfortunate graduate students participated in this trial
10:14:22AM and they aspirated out gastric contents at 20 minutes, 40 minutes
10:14:27AM and 60 minutes. I'm glad I wasn't the grad student in that
10:14:27AM study.
10:14:35AM But what they showed is that at 20 minutes was the
10:14:38AM first time they were able to put a tube down and take samples
10:14:41AM out, is that you can see the pH range is pretty wide and this
10:14:47AM makes sense because you start with 250 ML of gastric fluid at,
10:14:53AM roughly, pH 2 to 2.2, 2.3, and then you add about an equivalent
10:15:00AM volume of water, which is typically 7. All right
10:15:04AM So what's halfway between 2 and 7; 4 and a half. So it
10:15:09AM makes a lot of sense you're going to get there. So what she
10:15:11AM showed is that yeah, about the 75th percentile was right around 4
10:15:16AM and a half. And you can see that if you were to do some sort of
10:15:22AM a regression looking backwards towards the Y axis, you'd be up
10:15:29AM around that 4 and a half. So -- and there are other -- other
10:15:36AM people that have reproduced this.
10:15:39AM Q. Dr. Rudnic, before we move on to the next slide, at your
10:15:42AM deposition you were asked if you found any other article that
10:15:45AM corroborated Kalantzi. Do you recall that?

10:15:48AM A. Yes.
10:15:48AM Q. And did you find one?
10:15:50AM A. Yes.
10:15:57AM Q. Let's go to Slide 14, please.
10:16:03AM Dr. Rudnic, what conditions did Lupin use in its
10:16:08AM bioequivalence studies?
10:16:10AM A. Well, they did exactly what the FDA required them to do,
10:16:13AM which is they had to administer 240 MLs of water to the subject,
10:16:19AM when they took either Oracea or their ANDA product and -- before
10:16:24AM they started testing. So time zero they took 240 MLs of water
10:16:30AM and whatever test product they were about to start testing.
10:16:35AM Q. Now, why is that important?
10:16:37AM A. Because a person of skill in the art would know that pH 4.5
10:16:41AM is physiologically relevant stomach pH and subjects would have a
10:16:48AM median pH of 4.5 upon drug administration immediately.
10:16:52AM Q. Let's all turn to PTX-191 in your witness book, Dr. Rudnic.
10:16:59AM This is tab 8.
10:16:59AM A. Yes.
10:17:00AM Q. Do you recognize this document?
10:17:02AM A. Yes.
10:17:03AM Q. Can you tell us what it is?
10:17:04AM A. This is the report synopsis for the Lupin bioequivalence
10:17:08AM study, that we were just talking about.
10:17:12AM Q. Did you consider PTX-191 in forming your opinions in this
10:17:14AM case?

10:17:14AM A. Yes.

MR. COCHRAN: Your Honor, Plaintiffs would like to offer PTX-191 into evidence.

THE COURT: Objection?

MR. RAKOCZY: Subject to our Daubert motion, Your Honor, no objection.

(Exhibit Number PTX-191 was admitted.)

THE COURT: You developed seven drugs. Did you test each and every one of them at 4.5 pH?

THE WITNESS: Yes, sir. Yes, Your Honor.

THE COURT: As part of the approval process?

THE WITNESS: Many times, yes. Yes, Your Honor.

BY MR. COCHRAN:

Q. Dr. Rudnic, let's move on to another topic of scientific background. What is an absorption, window?

A. So drugs in order to get into the bloodstream have to be absorbed. If they are absorbed at a certain part of your intestinal tract, at a very high degree, but yet before that area and after that area, you find a decrease, significant decrease in absorption. The area of high absorption is considered to be called an absorption window. All right. So these occur for many drugs. There are some drugs where they don't occur, but for doxycycline, yes.

Q. So doxycycline has an absorption window?

A. It sure does.

10:18:31AM Q. How do you know?
10:18:32AM A. Well, first of all, in every single case that I have done
10:18:36AM with Oracea over the years, the opposing side has thrown at us
10:18:41AM dozens of articles or book chapters talking about how there is an
10:18:47AM absorption window for doxycycline. And in fact, most of these
10:18:51AM articles talk about in generalities about how it's in the upper
10:18:55AM part of the GI tract and there's one in particular that talks
10:18:58AM about it being in the duodenum.
10:19:00AM THE COURT: Just a moment. Let's go over some basic
10:19:04AM physiology here. So the gastric is the adjective for stomach.
10:19:09AM The pylorus is the exit from the stomach into the duodenum?
10:19:12AM THE WITNESS: Yes.
10:19:13AM THE COURT: The duodenum is the beginning of the small
10:19:15AM intestine?
10:19:15AM THE WITNESS: Yes.
10:19:16AM THE COURT: What are the parts that you count as the
10:19:19AM distal small intestine?
10:19:21AM THE WITNESS: The Jejunum and the ilium. So it goes,
10:19:23AM Your Honor, the stomach is not an absorptive organ.
10:19:23AM THE COURT: Okay.
10:19:29AM THE WITNESS: The purpose of the stomach is to take
10:19:33AM acid and enzymes and break down proteins into amino acids so that
10:19:41AM your body can then absorb them in your intestinal tract. And
10:19:44AM then you can reassemble them into proteins that your body then
10:19:48AM needs.

10:19:49AM THE COURT: So the entirety of the small intestine
10:19:54AM compromise of the duodenum, the jejunum and ilium?
10:19:58AM THE WITNESS: Yes. And then you go to the large
10:19:59AM intestine and the colon.
10:20:01AM THE COURT: Colon is a synonym for the entire large
10:20:05AM intestine?
10:20:06AM THE WITNESS: Correct. Gastroenterologists might have
10:20:13AM slight issue with me there, but not much.
10:20:14AM BY MR. COCHRAN:
10:20:14AM Q. What else can you tell us about doxycycline absorption
10:20:17AM window?
10:20:18AM A. Well, in general this absorption window was known, but we
10:20:24AM didn't know how much of an absorption window there was until the
10:20:28AM folks that developed Oracea did what's called scintigraphic
10:20:33AM study. And I've done about 12 scintigraphic studies in my
10:20:38AM career.
10:20:38AM These are really specified high level and very
10:20:41AM expensive studies. What you do is you radio label the drug and
10:20:47AM you then can follow it using gamma scintigraphy as to where the
10:20:53AM drug is being absorbed in regions of the GI tract. And for the
10:20:57AM first time, the folks at -- who developed Oracea, show that all
10:21:01AM the literature in animal studies earlier was correct. Most of
10:21:07AM the absorption does, indeed, occur in the early small intestine
10:21:11AM in the duodenum.
10:21:12AM But when you go to the jejunum and the ilium, you drop

to less than half. And then you go to the colon and you're below 5 percent. So this is a fairly, I would call, pronounced absorption window.

BY MR. COCHRAN:

Q. So let's go to PTX-176 in your witness book. This is tab 9.

A. Yes.

Q. Do you recognize this document?

A. Yes.

Q. Is this the Scintipharma study you were just referring to?

A. Yes.

MR. COCHRAN: Your Honor, Plaintiffs would like to offer PTX-176 into evidence.

MR. RAKOCZY: No objection, Your Honor.

THE COURT: Admitted.

(Exhibit Number PTX-176 was admitted.)

BY MR. COCHRAN:

Q. Dr. Rudnic, how is doxycycline absorption's window relevant in this case?

A. Well, it's important to put this in the context of the Chang patents. So the objective of Chang was to achieve a steady state blood level high enough to be effective to have a beneficial effect on the treatment of rosacea, which is reddening of the skin. It's a type of acne. But not high enough to exert an antibacterial effect. So at 0.1 micrograms per mL, it's been well shown that you start to have an antiinflammatory effect

10:22:35AM which calms down the redness in the face for rosacea.

10:22:42AM However, at 1.0 micrograms per mL, right around there,
10:22:44AM you start to get antibiotic effect. Now remember, this is a
10:22:48AM product you'll probably take for the rest of your life, as long
10:22:52AM as you have rosacea. And if you were take an antibiotic every
10:22:55AM day, you would ultimately develop a superinfection in your gut
10:22:59AM and that is a life threatening condition.

10:23:01AM THE COURT: This will not kill off gut flora. This
10:23:04AM will not lead to resistant superbugs or anything like that?

10:23:07AM THE WITNESS: Correct. So as long as you stay within
10:23:09AM that range. And this is -- this is what the folks that developed
10:23:16AM Oracea found, is that that can only be achieved with a very
10:23:20AM specific ratio of 30:10 IR/DR. In fact, too much DR will
10:23:28AM overshoot that absorption window and you will have lower
10:23:31AM bioavailability. If you have too much IR, you'll peek too soon
10:23:36AM and you won't last as long and maintain that antiinflammatory
10:23:42AM effect for 24 hours.

10:23:43AM So this is an absorption window that's very tight for a
10:23:46AM drug that has to have a very narrow window or you're going to
10:23:49AM start creating an antibiotic effect, you're going to create
10:23:52AM resistant bacteria, a superinfection, all sorts of bad stuff.
10:23:57AM All right? So important that you maintain it within this level,
10:24:00AM but also you're dealing with a drug that is very, very pronounced
10:24:05AM absorption window. You have to be very, very precise.

10:24:05AM

10:24:05AM BY MR. COCHRAN:
10:24:08AM Q. What else might happen if you have too much immediate
10:24:11AM release doxycycline?
10:24:14AM A. Well, again, you would have the concern of antibiotic effect
10:24:20AM because you probably would breach that 1.0 micrograms per mL. In
10:24:26AM fact, when they did some in silico modeling, the facts that
10:24:30AM developed Oracea showed that.
10:24:32AM Q. Let's move on to another topic. What is your definition of
10:24:37AM a person of ordinary skill in the art?
10:24:41AM A. Well a POSA or a person of ordinary skill in the art is a
10:24:46AM person with education and experience in drug delivery and
10:24:49AM formulation science as it relates to what we are talking about
10:24:52AM here. And that person could be any person with a Bachelor's
10:24:57AM degree with many years of experience or somebody with a higher
10:25:01AM degree with lesser years of experience. And obviously, the kind
10:25:05AM of experience matters, so relevant work experience.
10:25:10AM Q. And what, if anything, did you rely on when forming your
10:25:13AM definition of a POSA?
10:25:15AM A. My 40 years of working shoulder to shoulder with men and
10:25:19AM woman that have various educational degrees in various
10:25:25AM disciplines of pharmaceutical development and I think this one
10:25:30AM works just fine.
10:25:31AM Q. And did you rely on this definition in forming your opinions
10:25:34AM in this case?
10:25:35AM A. I did.

10:25:36AM Q. And Dr. Rudnic, what are those opinions?
10:25:40AM A. Well, the opinions can be boiled down to one statement is
10:25:44AM that Lupin's ANDA product infringes the Chang patents literally
10:25:48AM and under the doctrine of equivalents. And by the Chang patents,
10:25:52AM I mean US 8206740 and 7749532, what I call the Chang 740 and
10:26:01AM Chang 532 patents.
10:26:01AM Q. And what have you relied on in forming your infringement
10:26:05AM opinions in this case?
10:26:06AM A. Well, obviously the Chang patents. The Oracea NDA. Other
10:26:12AM documents associated with their ANDA. The Lupin ANDA, documents
10:26:16AM associated with their ANDA, documents provided by Lupin.
10:26:20AM Literature. FDA guidances. USP standards and Court's Claim
10:26:30AM Constructions of the terms that are in the Chang patents.
10:26:35AM Q. And have you considered the opinions of Ms. Vivian Gray and
10:26:38AM Dr. Graham Buckton on infringement?
10:26:41AM A. Yes.
10:26:41AM Q. Do you agree with those opinions?
10:26:43AM A. On infringement, generally, no.
10:26:46AM Q. Let's go to PTX-001 as well as 002. These are tabs 10 and
10:26:52AM 11 of the witness book.
10:26:52AM A. Yes.
10:26:54AM Q. Do you recognize these documents?
10:26:56AM A. Yes.
10:26:57AM Q. What are they?
10:26:58AM A. This is the Chang 532 patent and the Chang 740 patent.

10:27:03AM Q. And have you reviewed these patents in forming your opinions
10:27:06AM in this case?
10:27:07AM A. Yes.
10:27:09AM MR. COCHRAN: Your Honor, Plaintiffs would like to
10:27:10AM offer PTX-001 and 002 into evidence.
10:27:14AM THE COURT: I take it there's no objection?
10:27:15AM MR. RAKOCZY: No objection.
10:27:16AM THE COURT: Admitted.
10:27:16AM (Exhibit Numbers PTX-001 and PTX-002 were admitted.)
10:27:16AM BY MR. COCHRAN:
10:27:18AM Q. What claims of the Chang patents are being asserted against
10:27:22AM Lupin?
10:27:24AM A. In the Chang 740 patent claims, 1 and 20 are being asserted
10:27:28AM and in the Chang 532 patent claims, 1 and 16 are being asserted.
10:27:33AM Q. Walk us through Claim 1 of the 740 patent, please.
10:27:36AM A. Sure. In Claim 1 of the 740 patent it starts out as an oral
10:27:41AM pharmaceutical composition of doxycycline.
10:27:44AM Q. What's the next limitation?
10:27:46AM A. Says, once daily dosage that will give a steady state blood
10:27:50AM levels of doxycycline of a minimum of .1 micrograms per mL and a
10:27:58AM maximum of 1.0 micrograms per mL.
10:28:00AM Q. How about the next one?
10:28:01AM A. This is the composition consisting of immediate release or
10:28:04AM IR portion comprising of 30 milligrams of doxycycline.
10:28:08AM Q. And the next?

10:28:09AM A. Delayed release or DR portion comprising 10 milligrams of doxycycline.
10:28:13AM Q. And the last?
10:28:13AM A. And one or more pharmaceutical acceptable excipients.
10:28:15AM Q. Let's turn to your next slide. What have you shown here?
10:28:20AM A. Well, this contrasts the Claim 1 of both the 740 patent and the 532 patent. And they're really quite similar, but what you see in the Chang 532 patent is the word "about" appears before 30 milligrams doxycycline. And also that word "about" appears before 10 milligrams of doxycycline, referring to both the IR and DR components.

And then there's also a phrase that appears in the 532 patent in which the DR portion is in the form of pellets coated with at least one enteric polymer.

10:28:59AM Q. Let's go to your next slide. What have you shown here?
10:29:04AM A. These are claim 19 of the Chang 740 patent and claim 15 of the Chang 532 patent. And what you see here are method claims. And so these are for treating rosacea in a mammal and you see that claim 20 of the Chang 740 patent is a dependent claim says that mammal is a human. And claim 15 of the Chang 532 patent, similarly talks about treating rosacea in a mammal and the next dependent claim talks about that being a human.
10:29:38AM Q. Dr. Rudnic, how do the composition elements of these method of treatment claims relate to the composition elements we just discussed?

10:29:45AM A. They're identical, with the exception of, you know, the 532
10:29:49AM patent is slightly different than the 740 patent, but Claim 1 of
10:29:53AM each of those patents is very, very similar to what you see in
10:29:59AM these method claims.
10:30:00AM Q. Thank you for that. And why have you decided to focus on
10:30:02AM method of treatment claims?
10:30:04AM A. Well, if you look at Court's Claim Construction of these
10:30:07AM terms, both immediate release and portion construed to be
10:30:11AM functional limitations, but the claim construction of immediate
10:30:14AM release requires consideration of physiological conditions as
10:30:18AM we'll see in a minute.
10:30:19AM Q. Let's talk about those Claim Constructions. Next slide.
10:30:22AM What have you shown here?
10:30:23AM A. This is the Claim 1 of 740 patent where the word "immediate
10:30:28AM release" and IR has been construed by this Court to be the
10:30:35AM release that alters the subject steady state blood level of
10:30:39AM doxycycline.
10:30:40AM Q. Did you rely on this definition of immediate release in
10:30:43AM forming your opinions in this litigation?
10:30:45AM A. Yes.
10:30:46AM Q. Let's go to your next slide. What have you shown here?
10:30:51AM A. This is Claim 1 of 740 patent again where we talk about
10:30:55AM delayed release. And I rely on the Sun Court's construction
10:30:59AM where the release of a drug at a time other than immediately
10:31:02AM following oral administration.

Q. And did you rely on this definition of delayed release in this case?
A. Yes.
Q. Let's go to PTX-160, Tab 12 in your witness book.
A. Yes.
Q. Is this the Court's Claim Construction opinion in the Sun litigation that you were referring to?
A. Yes.
MR. COCHRAN: Your Honor, Plaintiffs would like to offer PTX-160 into evidence.
THE COURT: Any objection?
MR. RAKOCZY: One moment, Your Honor.
THE COURT: This is Judge Stark's opinion.
MR. RAKOCZY: I think it's odd to admit a Court decision.
THE COURT: It's odd to admit opinions as evidence. I mean, there's no objection you can consider it but I don't think it's technically evidence, but you may refer to it as governing law.
MR. RAKOCZY: Fair enough, Your Honor.
MR. COCHRAN: Thank you, Your Honor.
BY MR. COCHRAN:
Q. Let's turn to the next slide. What's your understanding of the portion term?
A. So this is -- the portion is a term that appears after

immediate release IR and after delayed release DR. And the Sun Court construed portion to mean any part of the claim composition that releases drug immediately upon administration. And delayed release to mean a part of the claim composition that delays release of drug until a time other than immediately following oral administration.

Q. And did you rely on these definitions of portion in this case?

A. Yes.

Q. And what did you rely on for coming up with these Claim Constructions?

A. The Court's Claim Construction.

Q. I was going to enter the Sun Court's post trial opinion, Your Honor. We don't necessarily need to.

THE COURT: I don't think it needs to be admitted into evidence, but I presume counsel have no objection to his referring to it and using it in his discussion. Just not technically evidence.

MR. RAKOCZY: No objection, Your Honor.

BY MR. COCHRAN:

Q. Let's go to your next slide. What's the definition of "about"?

A. About appears in the Chang 532 patent, as I mentioned earlier, and the Sun Court previously addressed the meaning of that claim term about. And also in that same opinion, Judge

10:33:27AM Stark noted that a POSA would understand that about 30 milligrams
10:33:32AM represents a range of 27 to 33 milligrams of doxycycline. In
10:33:37AM other words, a 10 percent variation or at most a range of 27 to
10:33:41AM 33 milligrams.
10:33:43AM Q. So let's go to your next slide. What do these Claim
10:33:47AM Constructions mean to you?
10:33:47AM A. The claim terms have been construed to have functional
10:33:51AM limitations, so how do these things function? So physiological
10:33:55AM conditions are relevant to the infringement inquiry.
10:33:59AM Q. Have you formed an opinion regarding whether Oracea is
10:34:02AM covered by the asserted claims of the Chang patents?
10:34:08AM A. Yes, I believe Oracea is a commercial embodiment of the
10:34:11AM Chang patents.
10:34:12AM Q. What did you base your opinion on?
10:34:13AM A. Well, Galderma holds a new drug application 50-805, Oracea
10:34:18AM capsules, which was approved by FDA on May 26 of 2006. And the
10:34:26AM prescribing label, which part of that ANDA shows that Oracea
10:34:30AM meets each and every limitation of the asserted claims.
10:34:33AM Q. Let's go to PTX-162 in your witness book. This is tab 14.
10:34:33AM A. Got it.
10:34:38AM Q. Do you recognize this document?
10:34:40AM A. Yes.
10:34:40AM Q. What is it?
10:34:41AM A. This is the Oracea label from their ANDA.
10:34:45AM Q. Did you consider PTX-162 in forming your opinions in this

10:34:49AM 1 case?
10:34:49AM 2 A. Yes.
10:34:50AM 3 MR. COCHRAN: Your Honor, Plaintiffs would like to
10:34:51AM 4 offer PTX-162 into evidence.
10:34:53AM 5 THE COURT: Any objection?
10:34:54AM 6 MR. RAKOCZY: No objection, Your Honor.
10:34:55AM 7 THE COURT: Admitted.
10:34:55AM 8 (Exhibit Number PTX-162 was admitted.)
10:34:55AM 9 BY MR. COCHRAN:
10:34:57AM 10 Q. Dr. Rudnic, what support did the Oracea label provide to
10:35:00AM 11 your understanding of the Oracea's formulation?
10:35:03AM 12 A. Well, that Oracea meets each and every limitation of the
10:35:08AM 13 asserted claims.
10:35:09AM 14 Q. Can you walk us through this claim.
10:35:11AM 15 A. Sure. What you see on the left is Claim 1 of the Chang 740
10:35:15AM 16 patent and on the right is the label from Galderma. In Claim 1,
10:35:19AM 17 you can see it's an oral pharmaceutical composition of
10:35:22AM 18 doxycycline and --
10:35:23AM 19 THE COURT: Can I ask? Does anyone dispute that Oracea
10:35:31AM 20 does embody the Chang patents?
10:35:35AM 21 MR. COCHRAN: We don't.
10:35:37AM 22 MR. RAKOCZY: We have not disputed it.
10:35:38AM 23 THE COURT: I didn't think that was a dispute. You can
10:35:39AM 24 walk through lightly, but I can read the slide. I don't think
10:35:41AM 25 there's any dispute here about Oracea in the Chang patents.

10:35:50AM MR. COCHRAN: Well, there is some evidence I would like to admit, then, Your Honor.

10:35:53AM THE COURT: Okay. Please.

10:35:53AM BY MR. COCHRAN:

10:35:59AM Q. Let's turn to tab 15. This is PTX-175.

10:36:04AM A. Yes.

10:36:05AM Q. What is this document?

10:36:07AM A. This is the clinical study report on multiple dose for Oracea that was in their ANDA.

10:36:14AM Q. Did you rely on this document in forming your opinions in this case?

10:36:16AM A. Yes.

10:36:18AM MR. COCHRAN: Your Honor, Plaintiffs would like to offer PTX-175 into evidence.

10:36:23AM THE COURT: Any objection?

10:36:24AM MR. RAKOCZY: No objection.

10:36:24AM THE COURT: Admitted.

10:36:24AM (Exhibit Number PTX-175 was admitted.)

10:36:24AM BY MR. COCHRAN:

10:36:28AM Q. Let's go to slide 39, please. Let's talk about Lupin's product. First let's turn to PTX-198 in your exhibit book. This is tab 16.

10:36:40AM A. Yes.

10:36:41AM Q. Do you recognize this document?

10:36:42AM A. Yes.

10:36:43AM

10:36:44AM Q. What is it?
10:36:45AM A. This is the Lupin prescribing label that was in their ANDA.
10:36:49AM Q. And did you rely on this document in forming your opinions
10:36:51AM in this case?
10:36:52AM A. Yes.
10:36:54AM MR. COCHRAN: Your Honor, Plaintiffs would like to
10:36:55AM offer 198 into evidence.
10:36:58AM THE COURT: Any objection?
10:36:59AM MR. RAKOCZY: No objection.
10:36:59AM THE COURT: Admitted.
10:36:59AM (Exhibit Number PTX-198 was admitted.)
10:37:00AM THE COURT: Am I right there's no dispute there is oral
10:37:04AM composition of doxycycline. That there is no dispute that there
10:37:07AM is a once daily dosage with steady stream of .1 milligram and 1.0
10:37:14AM and that there are excipients here?
10:37:16AM MR. RAKOCZY: We do not dispute those facts, Your
10:37:18AM Honor.
10:37:18AM THE COURT: We can move over those things lightly, the
10:37:22AM heart of this case is about is this 30:10 or --
10:37:26AM MR. COCHRAN: Right. And I'd also like to point out
10:37:26AM that there is no dispute that there is, in fact, an immediate
10:37:28AM release portion and a delayed release.
10:37:30AM THE COURT: There is no dispute that there is immediate
10:37:32AM release portion. Now the size of those is in dispute.
10:37:36AM MR. RAKOCZY: Exactly, Your Honor. Thank you. We

10:37:37AM agree there's a 22 milligram immediate release and 18 milligram
10:37:41AM delayed release, Your Honor.
10:37:41AM THE COURT: Right.
10:37:42AM MR. RAKOCZY: Their position is obviously the 18 has to
10:37:45AM be segmented or understood differently.
10:37:45AM BY MR. COCHRAN:
10:37:53AM Q. Let's go on to Slide 45 and let's talk a little bit more
10:37:58AM about the design and function of Lupin's ANDA product.
10:38:02AM Dr. Rudnic, what have you shown here on Slide 46?
10:38:07AM A. Well, this is a roadmap for what I'm going to talk about.
10:38:12AM One, Lupin designed its ANDA product to have a weak enteric coat
10:38:16AM and the design of that results in a 30:10 composition ratio. And
10:38:22AM as a result their ANDA product infringes the Chang patents.
10:38:26AM Q. Let's talk about how Lupin designed its ANDA product. On a
10:38:30AM high level, how does Lupin manufacture its product?
10:38:33AM A. You can see here it's a lot of unit operations, so it's a
10:38:38AM fairly complicated process to manufacture. But basically can
10:38:43AM come down to five stages, as Lupin calls it, sugar hardening
10:38:48AM stage. You start coating on a sugar sphere, they harden that.
10:38:52AM Then they load the drug, then they coat that and then they
10:38:56AM enteric coat and they fill in capsules.
10:38:59AM THE COURT: Why sugar? It just provides a useful kind
10:39:03AM of like the nub of a pearl?
10:39:05AM THE WITNESS: It's uniform, Your Honor. So the -- I've
10:39:08AM done this quite a few times. If you try to create a pellet on

10:39:11AM its own, they're rough, they don't always look spherical. These
10:39:16AM sugar spheres are used in nonpareils in candy and confections.
10:39:21AM And maybe as a child you might have seen them. And manufacturers
10:39:26AM deliberately will take certain sieve sizes, certain particle size
10:39:32AM cuts, so they're really quite tight in terms of particle size.
10:39:34AM Now, When you coat spheres, what's really important is
10:39:38AM particle size distribution. And so if you start with things that
10:39:41AM are almost perfectly spherical and perfectly identical in terms
10:39:47AM of size, at least you're starting from a good place.
10:39:47AM BY MR. COCHRAN:
10:39:52AM Q. I'd like to offer a few exhibits into evidence and I'll try
10:39:56AM and shortcut this as much as possible. Let's turn to PTX-184,
10:40:01AM Tab 17 in your witness book.
10:40:01AM A. Yes.
10:40:03AM Q. Do you recognize this document?
10:40:04AM A. Yes.
10:40:05AM Q. What is it?
10:40:05AM A. This is the overall quality summary of the drug product from
10:40:10AM the Lupin ANDA.
10:40:11AM Q. Let's turn to the next tab, Tab 18. This is PTX-185.
10:40:16AM Do you recognize this document?
10:40:17AM A. Yes.
10:40:18AM Q. What is it?
10:40:19AM A. This is an excerpt from the product development report which
10:40:24AM is known as 3.2.P.1 and basically it's a description and

composition of the drug product for Lupin's ANDA product.
Q. And did you rely on PTX-185 in forming your opinions in this case?
A. Yes.
Q. Let's turn to the next tab, Tab 19. This is PTX-186.
Do you recognize this document?
A. I do.
Q. What is it?
A. This is the pharmaceutical development report for the Lupin ANDA product.
Q. And did you rely on PTX-186 in forming your opinions?
A. I did.
Q. Let's go to Tab 20, PTX-187.
Do you recognize this document?
A. Yes.
Q. What is it?
A. This is the manufacturing process development and process for Lupin's ANDA product.
Q. And did you rely on PTX-187 in forming your opinions in this case?
A. I did.
MR. COCHRAN: Your Honor, Plaintiffs would like to offer PTX-184, 185, 186, and 187 into evidence.
THE COURT: Mr. Rakoczy, any objection to any of those four?

10:41:24AM MR. RAKOCZY: No objection, Your Honor.
10:41:26AM THE COURT: And am I right that 198 already got moved
10:41:28AM in and admitted?
10:41:30AM MR. COCHRAN: I believe you are right.
10:41:32AM MR. RAKOCZY: Yes.
10:41:32AM THE COURT: We've admitted everything apart from the
10:41:36AM legal opinions and the Schneider article. Please proceed.
10:41:44AM MR. COCHRAN: Thank you, Your Honor.
10:41:44AM (Exhibit Numbers PTX-184, PTX-185, PTX-186, and
10:41:44AM PTX-187 were admitted.)
10:41:44AM BY MR. COCHRAN:
10:41:45AM Q. So what, if anything, stands out to you about how Lupin
10:41:48AM manufacturers its ANDA product?
10:41:50AM A. Two things strike me immediately. Number one, the use of
10:41:54AM methylene chloride and the percent weight gain at the enteric
10:41:58AM coat stage.
10:41:59AM Q. Why does methylene chloride concern you?
10:42:02AM A. First of all, I worked with methylene chloride early in my
10:42:05AM career. It smells awful. Anyone who's driven by a paint factory
10:42:10AM in New Jersey before 1988, probably smelled it from I-95. But
10:42:16AM methylene chloride has been found by the EPA to be an
10:42:20AM unreasonable risk to human health.
10:42:22AM It is not only that associated with neuro toxicity,
10:42:29AM liver toxicity, cancer and even death. I worked at Bristol Myers
10:42:34AM Squibb with a technician and he worked with methylene chloride a

long time before I got there and he died in his early 50s from liver failure. Didn't drink. And we always thought it was due to his exposure to methylene chloride and thankfully in the mid '80s water based latex coatings and latex paint became available. So by the late '80s, we switched over to water-based coatings.

THE COURT: So this was in common use?

THE WITNESS: Up until about 1984, Your Honor. And then the EPA came out and said -- and it started with the states. New Jersey was the first and then Washington state was the second.

THE COURT: But this is the EPA. FDA hasn't done anything about this?

THE WITNESS: They don't care, Your Honor.

THE COURT: Okay.

THE WITNESS: Sadly. Don't know. Call your Congressman.

So I would tell you that this was very, very concerning to me. Also the Centers For Disease Control consider this to be an occupational carcinogen. And so, putting a carcinogen into a pharmaceutical product raises a lot of questions and it was the first thing I saw when I -- when you contacted me and I looked at this. I said, Why would they possibly use methylene chloride in a pharmaceutical product today.

THE COURT: Is it common to use methylene chloride in pharmaceutical coasting processes in the United States?

10:44:10AM THE WITNESS: Not in coating processes where you're
10:44:12AM blowing it out the stack. And the other thing is --
10:44:14AM THE COURT: What is it common for?
10:44:18AM THE WITNESS: It is used in spray drying, Your Honor.
10:44:21AM And spray drying is very -- very controlled, absolutely contained
10:44:26AM environment. And they actually recover the solvent and reuse it.
10:44:32AM Nothing goes out into the atmosphere. Nothing is being exposed
10:44:35AM to the worker.
10:44:36AM THE COURT: Right, but is it being ingested by the
10:44:38AM person?
10:44:39AM THE WITNESS: No, because by vacuum they can pull off
10:44:44AM all the methylene chloride before it completely dries. Now, in
10:44:48AM coating something different happens. So they will blow it out a
10:44:54AM stack and they will use a scrubber to try to take out most of it.
10:45:00AM Now scrubbers at their best are 99 percent.
10:45:04AM THE COURT: How much is someone who is taking one of
10:45:06AM these pill ingesting methylene chloride?
10:45:09AM THE WITNESS: Trace amounts, Your Honor, but it's not
10:45:11AM zero.
10:45:12AM THE COURT: Right. And it's a lifetime drug?
10:45:13AM THE WITNESS: And it's a lifetime drug. So contrast
10:45:17AM that with Oracea where you have nothing but water-based coatings.
10:45:24AM This is unnecessary. There was no reason to do this and so
10:45:28AM knowing Oracea, knowing the fact that there's water-based
10:45:32AM coatings, I look at this and I go, why would you put this kind of

material in a drug product when you don't have to.

And I was accused of being biased against Lupin because of this. I said no, it just tells me this is an intentional thing. I really hope it was intentional, you know.

THE COURT: So the basis of your finding of intent that's the question raised. Keep saying they did this intentionally, but it's not like you have any direct evidence someone whispered or said it. It just looks crazy to you and you're inferring from that?

THE WITNESS: Absolutely, Your Honor. My brain is wired to do things safely and ethically and trying to treat patients in a way that I don't put any harm to them. I am not wired to think about what I need to do to succeed and maybe use a material that I shouldn't be using. They shouldn't be using this.

MR. RAKOCZY: Objection, Your Honor, relevance and this is not anywhere in his reports.

MR. COCHRAN: He did talk about methylene chloride and its effects on the workers and health risks in his expert report, Your Honor.

MR. RAKOCZY: He's not testifying about health risks to workers, Your Honor, he's now going into patients.

THE COURT: I am asking him what the basis is for assertion of intent, because of skeptical, there was no direct evidence of intent that -- he's answering why he has that in his

report. And so, you know, it's equivalent of responding to a question on cross. I'm allowing it

MR. COCHRAN: Thank you, Your Honor.

BY MR. COCHRAN:

Q. Now Before we move on, let's turn to PTX-135 in your witness book. This is Tab 221.

A. Yes. Got it.

Q. Do you recognize this document?

A. This is the excerpt from the CDC Centers For Disease Control and website talking about methylene chloride.

Q. Did you rely on PTX-135 in forming your opinions in this case?

A. Yes.

MR. COCHRAN: Your Honor, Plaintiffs would like to offer 135 into evidence.

THE COURT: Any objection?

MR. RAKOCZY: Objection. Relevance, Your Honor. This is not from the FDA. The FDA allows methylene chloride. They have very strict controls for it. I don't see that this has relevance.

THE COURT: I don't see what NIOSH. He touched generally on this being the kind of subject but this seems little far afield what NIOSH says about it.

MR. COCHRAN: Your Honor, this is from the CDC.gov website. There's a URL at the bottom.

10:48:09AM THE COURT: But it's about Occupational Safety & Health.

10:48:15AM MR. COCHRAN: This is something that he discussed in his expert report.

10:48:23AM THE COURT: I think this is getting a little far afield. Keep it out on 403 grounds.

10:48:25AM BY MR. COCHRAN:

10:48:31AM Q. Let's turn to PTX-136. This is tab 22.

10:48:37AM Do you recognize this document?

10:48:38AM A. Yes. This is the EPA document that says methylene chloride poses unreasonable risk to human health.

10:48:46AM Q. Did you rely on 136 in forming your opinions?

10:48:50AM A. Yes.

10:48:51AM Your Honor, we would like to offer PTX-136 into evidence.

10:48:53AM MR. RAKOCZY: Same objection. Number one, relevance, Your Honor. Number two, EPA has nothing to do with regulating drug products in the United States. And in fact, what the EPA says about methylene chloride, they specifically say does not apply to drugs, which is solely the jurisdiction of the FDA.

10:49:09AM MR. COCHRAN: There is relevance, Your Honor. This is part of Dr. Rudnic's opinions that he presented in his opinion.

10:49:14AM THE COURT: I believe he was discussing this in his deposition and his report, correct? You're not saying this is being sprung on us.

10:49:20AM MR. RAKOCZY: No, no, Your Honor, I'm saying relevance, number one. And number two, this is not anything to do with the FDA and the regulation of drug products.

10:49:29AM THE COURT: It's attenuated, but I will allow this as something that he talked about in his report. I think you have some very credible arguments that the weight I should give it is very limited, but I will allow it to go to weight and not admissibility.

10:49:47AM MR. COCHRAN: Thank you, Your Honor.

10:49:47AM (Exhibit Number PTX-136 was admitted.)

10:49:47AM BY MR. COCHRAN:

10:49:50AM Q. Now, Dr. Rudnic, did you form an opinion on why Lupin used methylene chloride?

10:49:56AM A. I am not sure why they used it, but the effect of using it was interesting. You'll see that they start with a methylene chloride coat in their sugar hardening stage. Then they go to a water coat for the drug stage and then another methylene chloride coat to seal the drug coat, followed by a water-based coat for the enteric coat and then fill in capsules.

10:50:22AM So they're stacking like on unlike coatings. Kind of like a sandwich, with very different types of coatings. In my view, you could argue this is to adequately seal the drug in the sugar. This is not necessary -- or you know, Oracea does this with water based coatings. So why you would select this particular solvent. To do this became very questionable to me

10:50:53AM until I saw this chart where I said, wow, they're stacking these.
10:50:58AM And coatings are kind of interesting. It's kind of
10:51:02AM like painting your wall with a latex paint. You wouldn't paint
10:51:06AM it on wax paper, because it will just peel right off. Well, when
10:51:10AM you have a coating, the polymer has to be able to adhere to the
10:51:16AM surface that it's being coated on or you'll have some space or
10:51:22AM some lack of adhesion. And it's primarily because methylene
10:51:28AM chloride and the kinds of things that -- the kinds of surfaces
10:51:33AM that set up with solvents don't allow for the polymers on top of
10:51:38AM it to actually penetrate and form a nice weave.
10:51:43AM Q. Dr. Rudnic, do you have any evidence that this like and
10:51:46AM unlike affects Lupin's pills?
10:51:50AM A. I can see from scanning electron images that Lupin provided.
10:51:56AM So here, you can see that with Oracea, which these are on the
10:52:00AM top, you can notice that where the blue arrows are there -- you
10:52:05AM can't see any difference between where the coating of -- you can
10:52:10AM see the talc and polymer coating there.
10:52:13AM You don't really see any difference between that and
10:52:16AM what's below it where there's no talc, of white specs, Your
10:52:20AM Honor. But you can see the coating and this is the lab scale
10:52:24AM batch that we're going to talk about a in a minute, but at least
10:52:28AM it's -- these images are instructive that even if this particular
10:52:33AM batch questionable lab scale batch, you can see that there's
10:52:38AM actual ridges of air that look like they occur in between one
10:52:44AM coating and the other.

10:52:47AM THE COURT: What is it that you understand to be air, the small little circular pocket?

10:52:52AM THE WITNESS: Well, not just the circular pockets, Your Honor. You can see that there seems to be -- so if you look at the bottom left, you'll note bottom left figure, you'll notice that the bottom arrow is pointing to an area between that talc and enteric coat and the area underneath it. So this is what I was saying about like applying paint to a wall. You want it to adhere to the surface below. That is not adhering to what's below it.

10:53:24AM BY MR. COCHRAN:

10:53:25AM Q. Let's turn to DTX-083. This is Tab 23.

10:53:32AM Do you recognize this document?

10:53:34AM A. Yes.

10:53:34AM Q. Is this the report that these MVA amendments came from?

10:53:38AM A. Yes.

10:53:38AM MR. COCHRAN: Your Honor, Plaintiffs would like to offer DTX-083 into evidence.

10:53:43AM THE COURT: Any objection?

10:53:44AM MR. RAKOCZY: No objection, Your Honor.

10:53:45AM THE COURT: Admitted.

10:53:45AM (Exhibit Number DTX-083 was admitted.)

10:53:45AM BY MR. COCHRAN:

10:53:47AM Q. Let's take a look at your next slide, Dr. Rudnic. What is percent weight gain?

10:53:51AM

10:53:52AM A. So percent weight gain is an average number. So if you were to take pellet and before you started the coating process that pellet was 100 percent of its weight. At the end of the coating process, if it were 30 percent heavier, you would say that it had a 30 percent weight gain.

Now this is important because in these coatings, and we're talking specifically about the enteric coating. There's a certain amount of that coating that is solid, principally the polymer and other parts that are water. Now this particular coating, Eudragit L30D55 is 30 percent solids. So 70 percent is water, going to come off. And 30 percent are solid that are going to be retained ideally on the pellet.

THE COURT: Come off when? During the manufacturing process?

THE WITNESS: Spraying the coating.

THE COURT: It's like a latex paint?

THE WITNESS: Exactly, but instead of putting it on with a brush or roller, you're spraying it on.

THE COURT: Got it.

And so what happens when you apply the coating to the entire pellet population?

THE WITNESS: Ideally you would like the pellets to be --

MR. RAKOCZY: Objection, Your Honor. This goes to our objection on the entire bell curve, it's a cartoon. We have no

10:55:19AM idea, there's no evidence if the bell curve looks like this, so
10:55:23AM just renewing our earlier objection.
10:55:26AM THE COURT: It's just a very general demonstrative or
10:55:31AM cartoon. I don't think that it's admissible to prove anything
10:55:35AM about the, you know, slope or shape or distribution or anything
10:55:38AM like that. It's just illustrating the idea of some kind of
10:55:43AM curve. And he's not saying it's precisely a normal distribution
10:55:47AM or bell curve and I don't think he has a basis to say that.
10:55:52AM MR. COCHRAN: That's right, Your Honor. This is just
10:55:54AM an exemplary bell curve on the slide and Dr. Rudnic is going to
10:55:56AM talk about what his opinion is on the distribution.
10:55:59AM THE COURT: Okay. But I would also like to know what
10:56:01AM the basis is for having a view of the distribution is that it is
10:56:05AM a normal or bell curve distribution, if you have any evidence?
10:56:10AM THE WITNESS: Actually, it could be a skewed
10:56:12AM distribution as well, depending on a lot of different aspects.
10:56:16AM THE COURT: If it's skewed then it's not a bell curve.
10:56:16AM THE WITNESS: Well, I understand that.
10:56:19AM THE COURT: Strictly speaking a bell curve, as
10:56:22AM mathematicians would talk about. This is just a figure of
10:56:24AM speech?
10:56:26AM THE WITNESS: It's less likely to be anything but a
10:56:27AM bell curve because we start with a sphere, Your Honor.
10:56:31AM THE COURT: I got it. And in nature lots of things
10:56:33AM turn into bell curves but we don't really know?

10:56:36AM THE WITNESS: It is -- I guess as a demonstrative the point I'm trying to make, Your Honor, is that some of these pellets will be less than the average and some of them will be more than the average. I am not trying to make any more detailed point than that.

10:56:50AM THE COURT: Okay.

10:56:52AM BY MR. COCHRAN:

10:56:53AM Q. So let's go to your next slide. What have you shown here, Dr. Rudnic?

10:56:59AM A. Well, that in terms of particle size, the Lupin ANDA product and the Oracea product use pellets that are presorted to be the same particle size.

10:57:06AM Q. And what weight gain would you expect for similar size pellets?

10:57:12AM A. You would have -- if they're similar size, you would expect, given the same coating, you would expect the same weight gain.

10:57:18AM Q. And did you look at the percent weight gain of Lupin compared to Oracea?

10:57:26AM A. Yes.

10:57:30AM Q. What did you observe?

10:57:31AM A. Well, I know that Lupin's is 18 percent. And what I'm about to testify is that 18 percent is light and that you can tell from the way it was selected that they selected the least possible coating they could get away with. So if you just simply think --

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10:57:54AM THE COURT: You can't tell us the least possible they

10:57:57AM could get away with. You can tell it's on the light side?

10:58:01AM THE WITNESS: I am about to show you, Your Honor, it's

10:58:03AM the least.

10:58:04AM THE COURT: Okay.

10:58:05AM THE WITNESS: So if it is the least, by logic some of

10:58:11AM the pellets that are less coated than the average will be less

10:58:15AM than weak.

10:58:19AM MR. RAKOCZY: Objection, Your Honor, to that line of

10:58:21AM testimony. And now showing, like I earlier objected to, we've

10:58:25AM now got two bell curves with different numbers at the top

10:58:30AM completely.

10:58:33AM THE COURT: There's a basis for, but idea is they

10:58:33AM overlap only a little bit and have normal distribution entailed.

10:58:38AM I'm not seeing anything and I still have not heard an explanation

10:58:42AM how it's the least. So I don't think you have a foundation for

10:58:45AM any of that. So maybe you want to go back or have him testify

10:58:48AM about how he knows it's less, the least possible.

10:58:52AM THE WITNESS: Perhaps I can just get out one concept,

10:58:55AM Your Honor, which is that a general principal in coating pellets

10:59:02AM is that when you have a functional coat in a modified release

10:59:06AM dosage form, the goal is to have as thick a coating as to ensure

10:59:11AM that all of your pellets are robust. This is a general concept.

10:59:16AM THE COURT: You are inferring from the fact it is so

10:59:19AM much lighter, there was some kind of intent to do something out

10:59:23AM of the ordinary?

10:59:24AM THE WITNESS: And I will show you from data, Your Honor, that I believe that.

10:59:26AM THE COURT: Okay. Show me the data.

10:59:27AM BY MR. COCHRAN:

10:59:27AM Q. Let's go to your next slide, Dr. Rudnic. What have you shown here?

10:59:30AM A. Lupin, in their batch records, show that they have an average weight gain of 18 percent at the enteric coating stage. Oracea has a 30 percent weight gain at the enteric stage.

10:59:34AM Q. Why is that important to you?

10:59:34AM A. Well, because I have commercialized 6 other delayed release products using Eudragit L30D55. Some of these were very, very broadly big sellers. Adderall XR and others. And all of them had more than 32 percent weight gain. Adderall XR had 40. So I am used to this polymer being coated to about 32 to 40 percent. So when I see 18 percent, that looks light to me. And so now I am worried about how it functions and how it delivers.

10:59:38AM Q. Okay. So how did Lupin select for that 18 percent weight gain?

10:59:43AM A. They did two things. They looked at in vitro testing and they looked at their scanned electronic images but primarily in vitro testing, quality control testing.

10:59:48AM Q. Let's start with in vitro quality control testing. What did they do?

10:59:49AM A. This is a QC test at pH 1.1. This test is meant to be a

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11:01:00AM stress test on enteric polymer. So you put it at pH 1.1. Keep
11:01:06AM it there for 2 hours and hope you don't see anything. And there
11:01:09AM are limits for that. So what you notice is that on their
11:01:12AM development batch, they started at a 17 percent weight gain and
11:01:17AM then went up by 2 percent increments. And they saw leakage at 17
11:01:22AM percent but did not see it at 19 or some of the other increasing
11:01:28AM percentages. Then they took a scale batch and did the same
11:01:35AM thing. Exposed it to the QC test for 2 hours at pH 1.1. And
11:01:40AM what you see at 16 percent, they had leakage. But at 18 percent
11:01:45AM and higher, they did not.
11:01:47AM THE COURT: That's what you mean by the lowest?
11:01:48AM THE WITNESS: So yeah. I think if 17 percent leaks and
11:01:54AM 16 percent leaks, 18 is about the lowest you can go and not see
11:02:00AM leakage. And I just want to remind you that this QC test is a
11:02:04AM mandatory pass for these kinds of products. So they have to pass
11:02:09AM this test. And so for them, they selected the least thick
11:02:15AM coating to pass the QC test.
11:02:18AM THE COURT: Why is there anything improper about that?
11:02:20AM THE WITNESS: Because if your least coating that will
11:02:25AM show no leakage is 18 percent, and there are going to be some
11:02:32AM pellets that are less than 18 percent because 18 percent is the
11:02:36AM average, then that means some pellets are going to leak.
11:02:40AM THE COURT: All right. But you don't have any evidence
11:02:41AM as to whether this is a normal distribution, squished
11:02:46AM distribution, flat distribution?

11:02:48AM THE WITNESS: No. What I do have is data at a pH on
11:02:54AM oral administration where I can show you that they do have
11:03:00AM release.
11:03:00AM BY MR. COCHRAN:
11:03:03AM Q. Let's move on to your next slide. What do the SEM images
11:03:09AM that Lupin provided you?
11:03:10AM A. So these particular pellets, these scanning electron images,
11:03:15AM were provided by Lupin. What you see is the development batch
11:03:19AM that we talked earlier, 17 percent weight -- excuse me. This is
11:03:24AM the -- yeah, this is the development batch, where they had 17
11:03:28AM percent weight gain. And what you will notice between that and
11:03:32AM 19 percent weight gain is that in the 17 percent gain you see
11:03:36AM some speckling there, that's talc in the coating. Talc has got a
11:03:41AM certain diameter, and it's flaky and all sorts of stuff. So when
11:03:46AM you don't have a very thick polymer coat, some of it tends to
11:03:50AM stick out. Well, this is important because talc is used in the
11:03:54AM coating so that these acrylic coatings don't stick to one another
11:03:59AM so you don't want that to happen because you might pull off some
11:04:02AM of the coating and that kind of defeats the whole purpose. So
11:04:05AM you put talc in it. That causes some imperfections. When you
11:04:10AM see the speckling that you see in that, there's channels along
11:04:13AM that talc because it doesn't adhere to the methacrylate coating.
11:04:19AM And in those channels, drug can escape. So what you want to do
11:04:24AM is have enough coating over and over so that you cover the talc
11:04:29AM and that talc no longer can give you those channels. And that's

what you see at the 19 percent weight gain.

Q. Dr. Rudnic, let's turn to PTX-202. This is Tab 24. Do you recognize it?

A. Yes, these are SEMs from scanned electron micrographs from the Lupin ANDA.

Q. Are these the ANDA images you were just referring to?

A. Yes.

MR. COCHRAN: Your Honor, Plaintiffs would like to offer PTX-202 into evidence.

THE COURT: Any objection?

MR. RAKOCZY: No objection, Your Honor.

THE COURT: Admitted.

(Exhibit Number PTX-202 was admitted.)

THE COURT: I think we should probably -- we have gone quite a while, and I think it is appropriate to take a 10-minute break and come back see if we can finish this up and take our lunch break.

(Break from 11:05 a.m. until 11:17 a.m.)

THE COURT: You may resume.

MR. COCHRAN: Thank you, Your Honor.

BY MR. COCHRAN:

Q. So Dr. Rudnic, now that we have talked about how Lupin designed its ANDA product, let's talk about how Lupin's product functions. How does Lupin's product function?

A. I believe it functions as a 30:10 IR DR composition.

11:18:06AM Q. And why do you say that?
11:18:09AM A. Well, you can see that part of what they call their DR
11:18:15AM portion actually releases immediately upon oral administration.
11:18:23AM And I believe it's because of their thin and weak enteric coat.
11:18:29AM And I believe that enteric coat is weak not only because of how
11:18:34AM thin it is but also because it's on an unstable platform of a
11:18:39AM methylene chloride coat.
11:18:41AM Q. So how do you know all of this?
11:18:45AM A. Well, there's two things. Mr. Avachat in his deposition
11:18:50AM says so. And secondly, I can take a look at Lupin's data from
11:18:54AM Lupin's ANDA that confirms those statements.
11:18:57AM Q. And what did Mr. Avachat say?
11:19:00AM A. Well, he said that the objective of their development was to
11:19:03AM develop a product that's equivalent in all aspects to Oracea.
11:19:06AM And when asked how he did that, he said they did whatever was
11:19:11AM required by the regulation to be equivalent in all aspects.
11:19:15AM Q. And what data did you rely on?
11:19:18AM A. Well, I took a look at their ANDA and the in vitro
11:19:25AM dissolution data at a biorelevant pH. This is also a QC test.
11:19:29AM And in vivo bioequivalence data in the context of doxycycline
11:19:34AM absorption window. And it was an objective of Lupin to obtain
11:19:39AM the desired drug release rate in order to make this product
11:19:42AM bioequivalence to Oracea using Mr. Avachat's words.
11:19:43AM Q. And before moving on, can you remind us what the Kalantzi
11:19:48AM article tells you?

11:19:49AM A. Well, Kalantzi says that the pH upon administration of a
11:19:53AM drug product with water will give you a pH of about 4 and a half.
11:19:59AM And as I said before, not only the Kalantzi article but common
11:20:05AM sense tells if you have a pH of about 2, and you are taking an
11:20:09AM equal volume of fluid at a pH of 7, the total fluid meets in the
11:20:13AM middle at pH 4 and a half. So and there are other articles out
11:20:17AM there that confirm that.
11:20:19AM Q. So let's go to Slide 67. How did this relate to --
11:20:23AM MR. RAKOCZY: Your Honor, I am going to object to the
11:20:25AM last portion of the testimony. That's just yet another attempt
11:20:27AM to try to wedge in the article that Your Honor excluded from
11:20:30AM Schneider. He was not allowed to testify at his deposition and
11:20:34AM instructed him not to answer. And he's now said twice other
11:20:38AM articles.
11:20:39AM MR. COCHRAN: He did not mention --
11:20:40AM THE COURT: I am going to allow it. I am going to
11:20:42AM allow it.
11:20:42AM BY MR. COCHRAN:
11:20:44AM Q. Let's go to Slide 67, Dr. Rudnic. How does that relate to
11:20:49AM what Lupin did?
11:20:50AM A. Well, Lupin did exactly what the FDA requires them to do.
11:20:54AM They administered 240 MLs of water with a test article either the
11:21:00AM Lupin ANDA product or Oracea at the time of bioequivalence
11:21:09AM testing.
11:21:10AM Q. Let's go to PTX-194 in your witness book. This is Tab 25.

11:21:16AM A. Yes.
11:21:17AM Q. What is this document?
11:21:19AM A. This is the clinical study report for the bioequivalence
11:21:25AM study that I talked about.
11:21:26AM Q. Did you consider PTX-194 in forming your opinions in this
11:21:30AM case?
11:21:30AM A. Yes.
11:21:31AM MR. COCHRAN: Your Honor, Plaintiffs would like to
11:21:32AM offer PTX-194 into evidence.
11:21:35AM MR. RAKOCZY: No objection, Your Honor.
11:21:36AM THE COURT: Admitted.
11:21:36AM (Exhibit Number PTX-194 was admitted.)
11:21:36AM BY MR. COCHRAN:
11:21:38AM Q. Dr. Rudnic, what does the mean of this data 4.5 reveal?
11:21:44AM A. The mean reveals they release exactly as Oracea which is
11:21:51AM undisputed 30:10 IR DR product.
11:21:55AM Q. And do you recall, Dr. Rudnic, that Lupin has accused you of
11:21:59AM calling 150 minutes immediate release?
11:22:05AM A. Well, this is a QC test. As I testified earlier and I am
11:22:12AM testifying right now, the time frame in these QC tests is not
11:22:16AM meant to mimic exactly the time frame in the body. It's a QC
11:22:22AM test. And each test is trying to figure something out, so you
11:22:26AM need to understand what it's trying to figure out. So in this
11:22:29AM particular case, the capsules are kept at pH 1.1 for 2 hours.
11:22:37AM This is a stress test. It's longer than the capsule will ever

reside in the stomach, so it has nothing to do with the time and the stomach or release or other things. Your stomach does a much better job of releasing than a USP dissolution apparatus. This is a big test tube, if you will, and it's got a little stirrer in there that revolves slowly.

THE COURT: This is a very strange graph. You say it's pH 1.1 for 20 minutes but you don't report any data from 20 minutes to 60 minutes. You jump from 0 to 150.

THE WITNESS: I am about to show you the individual data, Your Honor. What this shows you is that once you get to pH 4.5 -- and remember I said earlier that the FDA tells you for these modified release products you should test at, in fact, they want you to test at pH 4.5 all the way up to pH 7.5. So when you do that -- and that's the first time that you are changing from this pH 1.1 QC test to pH 4.5 QC test for another 2 hours, you will see that you have identical release at the very first time frame that Lupin takes a sample that happens to be at 30 minutes after you have changed the buffer. Once you change the buffer, it's like the clock starts over again. So this is 30 minutes after you have now exposed it to a higher pH. Now recall, Your Honor, that pH 1.1 is not a relevant pH in the stomach. It is actually a pH that is supposed to be a stress test.

THE COURT: But the FDA expects you to use it.

THE WITNESS: Absolutely.

THE COURT: You have used the 1.1 on your own

11:24:32AM 1 medicines?
11:24:33AM 2 THE WITNESS: Without a doubt, Your Honor. And it's a
11:24:35AM 3 useful QC test. But understand that whatever it releases in 2
11:24:39AM 4 hours does not equilibrate to whatever releases in the stomach
11:24:45AM 5 for those 2 hours.
11:24:46AM 6 The other thing to remember is that the polymer that's
11:24:48AM 7 being used here, and as the counsel for Lupin points out, it's
11:24:55AM 8 the same polymer. So the polymer in Oracea and the polymer in
11:24:59AM 9 Lupin's ANDA product is a product from Evonik called Eudragit
11:25:08AM 10 L30D55. Tough to say but German. What do you expect?
11:25:14AM 11 In that particular polymer, it has ammonium groups in
11:25:20AM 12 the acrylic acid side chains. These ammonium groups will ionize
11:25:29AM 13 at a certain pH 5.5. All right. And so if you hold it at pH
11:25:35AM 14 1.1, nothing should ionize, nothing should come out, and that's
11:25:41AM 15 why the QC test is so important. But as you start to go up
11:25:45AM 16 higher in pH and you come close to 5.5, about 5, the polymer will
11:25:50AM 17 start to ionize and will start to flake off and dissolve at pH
11:25:56AM 18 5.5, which is the pH in the duodenum.
11:25:59AM 19 THE COURT: Can you explain why that's the case?
11:25:59AM 20 THE WITNESS: Sure.
11:26:03AM 21 THE COURT: I mean, for someone who's not a chemist, it
11:26:05AM 22 makes far more sense that a more acidic environment would cause
11:26:08AM 23 it to dissolve. But we're not extremely acidic or extremely
11:26:13AM 24 basic. We're at something in between. Why is it dissolving more
11:26:17AM 25 easily at a moderate pH?

11:26:19AM THE WITNESS: So this is the crux of enteric polymers, Your Honor. So for something to go into solution, it needs to be ionized. In other words, water, which is an ionic type solvent likes ionic things. If it's not ionic, in other words, if it's not ionized at all, it will sit there like cement. And this is what the FDA wants to see from an enteric polymer. Put it in there for 2 hours, we should see nothing. So this is a stress test. You can leave it there for a day. I had Adderall XR samples over a weekend. Nothing. And that was much more sizable compound than this one. So the polymer itself at 1.1 is locked down. You should see no release which is why, when I look at the way that they selected the 18 percent weight gain, it was the least possible percentage they could without seeing any release at that pH 1.1. So then I don't know. You can keep it for 1 hour, 2 hours, 12 hours, doesn't matter. That polymer is locked down. But as the pH starts to go up, the ammonium groups start to become ionized. Once they're ionized --

THE COURT: Because ammonium is basic and --

THE WITNESS: That's right, Your Honor. Once you get to higher pH, the ammonium groups ionize and then it starts to flake off. So it's a very clever thing. And Eudragit was created by a German company. It basically replaced shellac, and I'm serious about this, in the pharmaceutical industry.

THE COURT: You mean shellac?

THE WITNESS: Yes, Your Honor.

11:28:21AM And shellac also ionizes and dissolves at higher pHs. Anybody who's ever varnished a boat knows it will last for only a certain amount of time and after a while it will flake off. So this is better than shellac. Okay?

11:28:40AM So the idea is that these QC tests are meant to test the integrity of this coating. And so what the FDA wants you to do is, okay, let's start testing at 4.5 because we know that a lot of these enteric coatings are designed to start releasing at 5.5. We should see no release at 4.5 because it's not ionized and we shouldn't see release.

11:29:07AM Then they want you to test it at 5 or 5.5. And I think they say 4.5 or go to 6.5. But they want to see a range of pH between 4.5 and 7.5. That's in an FDA guidance document 20 years old that I helped do for modified-release dosage forms. So anyway, so this testing basically tests the integrity and ionization of these polymers.

11:29:35AM BY MR. COCHRAN:

11:29:38AM Q. Dr. Rudnic, before we move on, did you create this graph on this Slide 68?

11:29:43AM A. No.

11:29:43AM Q. Who did?

11:29:45AM A. Lupin.

11:29:49AM Q. Let's go to your next slide and walk to the individual data. Go ahead.

11:29:55AM A. Okay. So what you see here is dissolution data from Lupin's

11:30:00AM ANDA. So these are Lupin's data but they are comparing
11:30:05AM themselves, the ANDA product, with Oracea.
11:30:15AM Q. What have you shown here in the green box?
11:30:18AM A. So what we show here is the initial part of this QC test
11:30:22AM where you have pH 1.1. And you see it runs for 2 hours. And
11:30:28AM what you will notice is that 55 percent of the Lupin's ANDA
11:30:36AM product is the immediate release pellet. So here their immediate
11:30:41AM release pellets are doing exactly what they are supposed to do.
11:30:44AM They are releasing. Doxycycline is soluble at pH 1.1 so it comes
11:30:49AM off very easily. You will notice that Oracea, which has 75
11:30:54AM percent or 30 milligrams of doxycycline, releases almost entirely
11:31:03AM its amount of immediate release pellets. So again, their
11:31:07AM immediate release pellets are doing exactly what they are doing.
11:31:10AM Both sets of immediate release pellets are releasing 100 percent
11:31:14AM of what they should be releasing. So no problem. No question
11:31:19AM here. This is exactly as you would expect.
11:31:21AM Q. Let's move on to the next part of the slide.
11:31:25AM A. So this is very interesting. So what you will notice is
11:31:30AM that this test then moves to pH 4.5. And remember, the time
11:31:36AM frames in this QC test have nothing to do with correlations to
11:31:40AM exactly in the GI tract. It's a QC test. And so what you have
11:31:45AM here in Oracea in green, no additional release from the Oracea.
11:31:51AM THE COURT: I am trying to understand these figures
11:31:52AM because you would have thought that the numbers would keep going
11:31:56AM up as more time passed yet on the bottom we have some lower

numbers after 150, 180 minutes.

THE WITNESS: Slightly lower. And it may be due to changing and eliminating some of the solution while adding in some buffer.

THE COURT: Oh, okay. Yeah.

THE WITNESS: But the important thing here, Your Honor, is that you are not getting additional release above what has already been released. In other words, the delayed release pellets of Oracea that are coated with Eudragit L30D55 are not releasing at pH 4.5. They are coated at 30 percent. However, pellets that are coated at 18 percent are releasing. In fact, all of them release a little bit and 5 of the 12 capsules are releasing quite a bit. And this is --

THE COURT: Numbers 1, 3, 6, 7, and 8?

THE WITNESS: Correct. And you can see at the end of this QC test, the average release is 75 percent. 75 percent of 40 milligrams is 30 milligrams, Your Honor.

THE COURT: Okay. Got it.

THE WITNESS: This should not happen if you have a good robust enteric coat of Eudragit L30D55. We don't see this with Oracea. We do see this with the Lupin product. And I will remind Your Honor, these data are from Lupin's ANDA. They certified to the FDA that these data were accurate, they were reliable, and they were released by the quality assurance unit. If these data were unexpected, in fact, if they looked at these

11:33:49AM compared to Oracea and they thought they had a problem, they were
11:33:52AM legally obligated to do an investigation. They were legally
11:33:56AM obligated to do a retest. They didn't.
11:33:59AM THE COURT: Okay. This is about the FDA. Got it. I
11:34:03AM understand that. The Court still has to decide how that bears on
11:34:06AM the meaning of the patent.
11:34:07AM THE WITNESS: Understood, Your Honor. I just want to
11:34:11AM talk about the function of their product, and I am using their
11:34:13AM data to do it.
11:34:13AM BY MR. COCHRAN:
11:34:15AM Q. Dr. Rudnic, what's the standard number of capsules that
11:34:18AM should be tested in vitro dissolution test?
11:34:21AM A. Typically no less than 6, and 12 if you want to do an
11:34:25AM instant repeat. So 12 is a more robust number than 6.
11:34:30AM Q. Does this impact your opinion at all?
11:34:34AM A. It solidifies my opinion that their so-called DR pellets are
11:34:39AM releasing at a pH 4.5 which is a pH, as I testified, that you
11:34:43AM will see in the stomach upon immediately upon oral
11:34:47AM administration.
11:34:48AM THE COURT: But you are saying this 150 figure, is that
11:34:53AM after 120 minutes of pH 1.1 plus 30 minutes of 4.5?
11:34:58AM THE WITNESS: Yes.
11:35:00AM THE COURT: Okay. So then for immediate for the
11:35:03AM immediate release, I should be looking at that row of 150 where
11:35:06AM the mean is 64 percent. 64 percent of 40 milligrams is about

11:35:17AM two-thirds. What is that? Like 26, 27?

11:35:21AM THE WITNESS: Yeah. So Your Honor, 30 milligrams, 30

11:35:25AM minutes into this test is not 30 minutes immediate release in the

11:35:30AM body. The time frames have no --

11:35:33AM THE COURT: I see. This is 30 minutes in vitro but you

11:35:36AM are saying in vivo it probably looks different.

11:35:39AM THE WITNESS: It almost certainly would. And the point

11:35:42AM is that a lot of the release that you see in vivo especially in

11:35:52AM the various parts of the intestinal tract are not correlated to

11:35:55AM these tests. These tests were never meant to tell you minute by

11:35:59AM minute how much --

11:36:00AM THE COURT: Quality control test. I got it.

11:36:04AM THE WITNESS: So it's important for us to understand

11:36:05AM the limitations of these tests. These are not meant to be

11:36:10AM completely indicative of what you will see in the body. So but

11:36:17AM what this does tell you, the information this test does tell you

11:36:21AM is that it releases 30 milligrams when it should only be

11:36:25AM releasing 22 milligrams. That's what these data tell me.

11:36:25AM BY MR. COCHRAN:

11:36:30AM Q. Now, Dr. Rudnic, did Dr. Buckton and Ms. Gray attempt to

11:36:35AM discredit these data?

11:36:36AM A. They did.

11:36:38AM Q. What is your understanding of their argument?

11:36:41AM A. Well, they called something called a hotspot. I mean, this

11:36:48AM is a ghost. This is not scientific. No one has ever proven that

it exists. Certainly nobody has ever proven that it can impact the way Eudragit L30D55 dissolves.

Q. Dr. Rudnic, what is a hotspot?

A. I am not sure. But from what they are talking about, it means that when you change the buffer, somehow all of this basic buffer ended up at the capsule and somehow it just blew up. This is not supported by science.

Q. Let's talk about that a little bit and let's go to PTX-223 in your witness book. This is Tab 26.

THE COURT: Perhaps you can also explain what exactly the hotspot theory is to understand what you are rejecting.

THE WITNESS: I will do my best, Your Honor. I am sure Dr. Buckton and Ms. Gray will probably have their own version of this. But I will tell you what I think it is. So you can -- when you have acid buffer in that QC test at pH 1.1 and you want to change it to pH 4.5, you have to do that by adding something with a higher pH. So when you do that, there has to be some mixing that occurs for it to become uniform. Before it becomes uniform, there may be spots where some of the pH is low and some of the pH is high. I will concede that that might happen for a second or two or 10 seconds but not for tens of minutes. And no one has ever shown that it actually exists to have an effect. My personal theory is that this is an excuse to retest a bad batch. So people generally don't like to fail a batch or recall a batch so they are desperate to find a reason to retest it. I believe a

11:38:51AM hotspot is a convenient excuse. That's my personal opinion.
11:38:51AM BY MR. COCHRAN:
11:38:55AM Q. Dr. Rudnic, let's look at the Miller paper.
11:38:59AM A. This paper in PTX-223 was written by someone named Dave
11:39:04AM Miller. And he was a student, graduate student in Bill Williams'
11:39:09AM lab at the University of Texas. I know both of them. I used to
11:39:13AM work with Dave Miller, and I used to work with Bill Williams. So
11:39:17AM what's interesting about this paper is that Dave -- and I didn't
11:39:23AM know this about Dave until we got into this case. But Dave had
11:39:28AM done some work using nuclear magnetic resonance technology. Lots
11:39:33AM of words there, but what it means is that they looked at the
11:39:36AM molecular basis of whether or not these things would mix quickly.
11:39:42AM And they looked at molecules, not just general pHs.
11:39:46AM And what they found is that the mixing occurs pretty
11:39:50AM much within seconds and that no difference in either slow -- so
11:39:57AM they did one slow where it took maybe 10, 15 minutes. And they
11:40:01AM did one normally and showed that there's no difference between
11:40:06AM the dissolution of this enteric polymer Eudragit L30D55 whether
11:40:14AM it's slow or fast.
11:40:15AM And the important thing here is that you have to
11:40:18AM remember there's 12 vessels that this analyst has to cover. They
11:40:24AM have 5 minutes, according to the USP method, to get that buffer
11:40:30AM into all 12. Wow. So you can imagine. You stop this and now
11:40:35AM you have 5 minutes to get the aliquot into each of these 12
11:40:42AM vessels. You better be quick. So they are probably more likely

11:40:45AM to be on the quick side than the slow side. So whatever it takes
11:40:49AM to equilibrate these two pH media will happen in seconds. And
11:40:56AM that's what the Miller paper shows.
11:40:57AM Q. Dr. Rudnic, did you rely on PTX-223 in forming your
11:41:03AM opinions?
11:41:03AM A. I did.
11:41:04AM MR. COCHRAN: Your Honor, Plaintiffs would like to
11:41:05AM offer PTX-223 into evidence.
11:41:08AM THE COURT: Any objection?
11:41:09AM MR. RAKOCZY: No objection, Your Honor.
11:41:10AM THE COURT: Admitted.
11:41:14AM MR. COCHRAN: Thank you.
11:41:14AM (Exhibit Number PTX-223 was admitted.)
11:41:14AM BY MR. COCHRAN:
11:41:15AM Q. Was Ms. Gray able to identify a hotspot in the Miller paper?
11:41:20AM A. No.
11:41:22AM Q. What did she say?
11:41:23AM A. She said a lot of things but she just circled the whole page
11:41:26AM so the whole thing was a hotspot.
11:41:28AM Q. What does that tell you?
11:41:30AM A. Well, there's no hotspot. And you can see at the bottom of
11:41:33AM the vessel where the capsules reside, quite uniform.
11:41:40AM Q. And what other challenges did Dr. Buckton and Ms. Gray make
11:41:43AM to the data presented?
11:41:49AM A. To be charitable, this is a questionable batch of --

11:41:58AM MR. RAKOCZY: Objection, Your Honor. This is opinions we saw nowhere in his reports.

11:42:02AM THE COURT: But this is for purposes of rebuttal. I mean, we technically could bring him back after the testimony. And it certainly seems more efficient to allow rebuttal now if that's acceptable to the parties.

11:42:04AM

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11:42:18AM MR. COCHRAN: I would also mention that this was all discussed in Dr. Rudnic's deposition.

11:42:19AM

11:42:21AM THE COURT: I'm going to allow it rather than having to bring him back in a day and a half.

11:42:24AM

11:42:28AM MR. RAKOCZY: Understood, Judge.

11:42:29AM THE WITNESS: Thank you, Your Honor. So Lupin had an opportunity to retest the existing ANDA batch, the one that was submitted to the ANDA. I mean, they had 230,000 capsules. I imagine they had a few of those laying around. And my understanding is that their excuse for not testing is, oh, it expired 2 months ago. Well, an interesting thing is that if they had tested, they could have extended the expiration date. So merely testing it again would have extended the expiration date. I don't believe they wanted to retest that ANDA batch.

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11:43:06AM

11:43:09AM THE COURT: That's speculation. Go on.

11:43:11AM THE WITNESS: I will move on to say, Your Honor, the batch they made in response to this litigation differs considerably from their ANDA batch. It is 6,000 capsules versus 240,000 capsules. The FDA would mandate you to do bioequivalence

11:43:14AM

11:43:21AM

11:43:27AM

test because the size of these batches are so different.

THE COURT: How do you know that the air flow particle dynamics of the polymer enteric spray rate were different for this batch? What tells you that?

THE WITNESS: There are two batch records that I looked at. One that was given to us a couple days ago which is the batch record for this batch and one from their ANDA. So I can look at all of these things. The spray rate is 10 fold. The air flow is 10 fold. I mean, I don't know what could be. The other thing is that their justification for this was that the manufacturer of the coating equipment says, well, there's a general scale-up parameter.

THE COURT: So you're criticizing their samples but you didn't run any tests yourself.

THE WITNESS: So Your Honor, the manufacturer says that that scale-up parameter that they used could vary by up to 20 percent, plus or minus 20 percent. So there's a lot of wiggle room here. And I have done scale-up my whole life, and I can tell you that you have to do a lot of different iterations in the process to figure out how they affect things.

THE COURT: So they didn't do it well, but you didn't do it at all.

THE WITNESS: I didn't have to, Your Honor. And the reason why I say I didn't have to is because you look at the performance of products to figure out if they are the same.

11:45:07AM THE COURT: You are looking at functionally how it works in vivo in blood streams but that's like outputs, not inputs. Got it.

11:45:17AM THE WITNESS: Sure. So the in vitro data at pH 4.5 is different between the ANDA batch that they submitted to the FDA and this batch which they didn't submit to the FDA and they didn't do bioequivalence testing. So what's going to happen is you are going to see some of the experts for Lupin get up and talk about how this batch is the same as the ANDA. It is not, in my opinion. It is different in terms of the way it's manufactured. And it functions -- it performs differently from based on the in vitro data. So for those things alone, I say it's different in a lot of different ways. And it would take a lot of research and a lot of time to figure out exactly how.

11:45:57AM BY MR. COCHRAN:

11:46:03AM Q. Let's go back to the data. What have you shown here?

11:46:08AM A. These are the plasma time curves for the Lupin ANDA product.

11:46:14AM THE COURT: We have a preserved Daubert objection here. It's understood. It's preserved for the record. But I am allowing this.

11:46:24AM MR. RAKOCZY: Thank you, Your Honor.

11:46:24AM THE WITNESS: Your Honor, it might be helpful if I explain what you are looking at. So these are plasma time curves or blood level curves in the vernacular of the bioequivalence study that was performed by Lupin. These are Lupin data. So

11:46:41AM what you have on the left is a standard plot. And that same
11:46:47AM data, the same set of data are plotted in a semi-log plot on the
11:46:54AM right.
11:46:54AM So semi-log plots take out any difference, so we will
11:46:57AM forget that for the moment. If you look at the chart on the
11:47:02AM left, what you see are two very similar curves. Now, for
11:47:11AM bioequivalence, what the FDA looks at are two measurements. One
11:47:18AM is the C-max or the peak concentration. So the peaks that you
11:47:23AM see pretty much at around 4 hours, 5 hours there. That point
11:47:31AM represents where the absorption of a drug product equals the
11:47:38AM elimination of the drug product.
11:47:40AM THE COURT: Show me which peaks you are talking about.
11:47:42AM The peak of the line at 6 hours on the left-hand graph?
11:47:47AM THE WITNESS: If you look at the left side of the left,
11:47:49AM you see the highest data points.
11:47:52AM THE COURT: Mean concentration so the highest blood
11:47:54AM concentration is getting 450 on the left-hand side and scale on
11:48:01AM the right.
11:48:02AM THE WITNESS: That's harder to read. But if you go to
11:48:05AM about 450 on the left side, you can see that that is the C-max,
11:48:13AM maximum concentration for both the Lupin ANDA product and Oracea.
11:48:20AM Now, the FDA takes that measurement, C-max and says that is a
11:48:26AM measure of the rate of drug absorption and release of a dosage
11:48:33AM form.
11:48:34AM THE COURT: There's some in vivo similarity here. The

11:48:36AM FDA cares about it. But it's not dispositive of the patent.

11:48:42AM THE WITNESS: I will leave that, Your Honor. I just want to finish my testimony that it is hard, very hard to be statistically the same for both the C-max and the area under this curve; two measurements for bioequivalence. And they did that not only for fasted but fed, a doubly-hard standard.

11:49:07AM So these products match both the rate and extent of drug absorption. Not my opinion. It's the FDA's opinion. Now, because the FDA says that these bioequivalence studies matter in terms of release of a drug substance, I can come to the conclusion that the Lupin ANDA product looks quite similar to a known and proven 30:10 IR DR.

11:49:44AM THE COURT: By the way, is the reference product here the Oracea and the test product is Lupin's?

11:49:50AM THE WITNESS: Correct. It's hard to make out because the graphs are so similar.

11:50:00AM THE COURT: Right. Okay.

11:50:00AM BY MR. COCHRAN:

11:50:02AM Q. Dr. Rudnic, let's go to PTX-190 in your witness book. This is Tab 27. Do you recognize this document?

11:50:09AM A. Yes.

11:50:10AM Q. What is it?

11:50:12AM A. This is Lupin's bioequivalence fasting study of doxycycline capsules that created the data that we just saw.

11:50:19AM Q. And did you consider PTX-190 in forming your opinions in

this case?
A. Yes.
MR. COCHRAN: Your Honor, Plaintiffs would like to offer PTX-190 into evidence.
THE COURT: Any objection?
MR. RAKOCZY: No objection, Your Honor.
THE COURT: Admitted.
(Exhibit Number PTX-190 was admitted.)
BY MR. COCHRAN:
Q. So Dr. Rudnic, moving on to your next slide, what have you concluded from the data in Lupin's own ANDA?
A. Doxycycline's narrow absorption window requires a specific ratio of IR DR. I know this from the Oracea NDA, all the studies that they did in developing Oracea. The scintigraphic study that I talked about. 30:10 is what's needed. And you can't get off far from 30 milligrams IR and still be bioequivalence to Oracea. That is very clear from the data in the Oracea NDA. What I showed just recently is that Lupin's doxycycline has a so-called DR component but 8 milligrams or 75 percent in total or 30 milligrams gets released at a pH immediately following oral administration. And 22 milligrams plus 8 milligrams equals 30. So I am testifying today that I believe Lupin's doxycycline product is a 30 milligram IR 10 milligram DR.
THE COURT: Dr. Rudnic, let me go back to a basic anatomical question. Say you take an average pill like the kind

you develop. You told me from the time you ingest a pill with what, a quarter liter of water, to the time it makes it to the bottom of the stomach the polymer is about an hour?

THE WITNESS: Yes.

THE COURT: Can you generalize about how long that pill spends in the duodenum, how long it spends in the jejunum, the ilium, and the colon. Is there like a standard figure or a range of figures that you were to ballpark it?

THE WITNESS: Sure. So the duodenum probably about an hour and a half.

THE COURT: So 1.5 hours in duodenum.

THE WITNESS: It could be less. It could be less if there were food moving it along.

THE COURT: So some drugs are instructed to take with food, and that's going to affect it. And others you are told don't take it within a couple of hours of a meal.

THE WITNESS: That's this one.

THE COURT: This one is don't take with food.

THE WITNESS: That's right.

THE COURT: If you don't take it with food, how long does it spend in the duodenum?

THE WITNESS: Probably about an hour at the most.

THE COURT: Up to one hour if no food. Okay.

THE WITNESS: And then comes the jejunum and ilium. And that depends, but that could be anywhere from 2 hours to 6

11:53:11AM hours.

11:53:12AM THE COURT: 2 to 6 hours assuming you haven't ingested
11:53:16AM food right then?

11:53:17AM THE WITNESS: That's right.

11:53:18AM THE COURT: And then the colon.

11:53:19AM THE WITNESS: And then the colon. It could be in the
11:53:21AM colon for a day or two. And it depends on again food. So mother
11:53:28AM nature is pretty good at getting rid of waste and food, so it
11:53:32AM moves things along if you have a lot of --

11:53:35AM THE COURT: Right. So your testimony was that the
11:53:37AM absorption rate is very high in the duodenum like in the 80s.

11:53:37AM THE WITNESS: Yes.

11:53:44AM THE COURT: And then falls to the 30s. I don't know if
11:53:44AM it was 37 or --

11:53:50AM THE WITNESS: Almost 90 percent in the duodenum. And
11:53:50AM about 37 --

11:53:54AM THE COURT: 37. So 37, 38 in the ilium in the jejunum
11:53:58AM but there's up to an hour for the medicine to be ingested into
11:54:00AM the duodenum. So you know there's bioequivalence in terms of how
11:54:05AM long it lasts and the figures were for, you know, hour, hour and
11:54:10AM a half at a pH of 4.5 or whatever. But you can't say like at
11:54:15AM what point in the duodenum this is all dissolving. What's the pH
11:54:19AM in the duodenum?

11:54:21AM THE WITNESS: 5.5, Your Honor.

11:54:24AM THE COURT: 5.5. Stomach you said there was a range,

11:54:26AM you said 3 was like --
11:54:27AM THE WITNESS: Anywhere from 2 to 5, and let's call it 3
11:54:31AM in the middle.
11:54:32AM THE COURT: 2 to 5 pH. And then 5.5 pH in duodenum.
11:54:40AM And what would you say the pH is in jejunum and ilium?
11:54:44AM THE WITNESS: Jejunum probably about 6. Slightly
11:54:48AM higher.
11:54:51AM THE COURT: And the ilium?
11:54:52AM THE WITNESS: About 6 and a half to 7 depending on what
11:54:56AM kind of diet you typically have. High fiber diets are slightly
11:55:04AM higher.
11:55:06AM THE COURT: These figures are going to hold basically
11:55:08AM true for medicines that are not ingested with food.
11:55:08AM THE WITNESS: That's correct.
11:55:12AM THE COURT: That's helpful. I do not have the benefit
11:55:18AM of premed or biochem background. Thank you.
11:55:18AM THE WITNESS: Understood, Your Honor. You're welcome.
11:55:18AM BY MR. COCHRAN:
11:55:22AM Q. Dr. Rudnic, what's the current status of Lupin's ANDA at the
11:55:28AM FDA?
11:55:29AM A. It is tentatively approved.
11:55:33AM Q. Let's go to PTX-049, Tab 28.
11:55:33AM A. Yes.
11:55:34AM Q. Do you recognize this document?
11:55:35AM A. I do.

11:55:35AM Q. What is it?
11:55:36AM A. It's the tentative approval letter from the FDA to Lupin for
11:55:40AM their ANDA.
11:55:42AM Q. Did you consider PTX-049 in forming your opinions in this
11:55:47AM case?
11:55:47AM A. I did.
11:55:48AM MR. COCHRAN: Your Honor, Plaintiffs would like to
11:55:50AM enter PTX-049 into evidence.
11:55:53AM THE COURT: Any objection?
11:55:53AM MR. RAKOCZY: No objection.
11:55:54AM THE COURT: Admitted.
11:55:54AM (Exhibit Number PTX-049 was admitted.)
11:55:54AM BY MR. COCHRAN:
11:55:56AM Q. All right. Let's go to your next slide. What conclusions
11:55:59AM have you drawn based on all the data and Lupin's own ANDA?
11:56:02AM A. My conclusion is that Lupin's ANDA product infringes the
11:56:06AM Chang patents.
11:56:07AM Q. Let's talk about your opinions on infringement. Let's go to
11:56:11AM the next slide. Can you walk us through this claim in relation
11:56:15AM to your --
11:56:17AM A. This is claim one of the Chang 532 patent, and you can see
11:56:20AM that it starts as an oral pharmaceutical composition of
11:56:25AM doxycycline. And on the right, I have Lupin's label and you can
11:56:28AM see doxycycline for oral use and it's 40 milligrams once daily.
11:56:37AM THE COURT: We can go through 076, 077, 078. None of

those is really in dispute. Why don't we go to 079.

MR. COCHRAN: Understood, Your Honor.

BY MR. COCHRAN:

Q. What are we showing here?

A. This is Claim 1 of the Chang 532 patent. Again, composition consisting of an immediate release IR portion comprising a drug wherein the drug consists of about 30 milligrams doxycycline. My contention and my testimony today is that because they have a like unlike layering of coatings which in my view is a fragile platform and a very light weight gain, they have designed a product that will leak, and it leaks at pH 4.5 which is where you are going to see the pH at the time of oral administration. They release 30 milligrams of doxycycline at that pH. 75 percent of the product. And the in vivo data they have is remarkably similar bioequivalence data to Oracea and undisputed 30:10 IR DR product.

Q. In your opinion, does Lupin's ANDA product meet this claim limitation?

A. Yes.

Q. Let's move on to the next slide. Have you formed an opinion on whether this claim element is met under the doctrine of equivalents?

A. Yes, it's insubstantially different from a pharmaceutical composition containing a 30 milligram IR portion.

Q. Why do you say that?

11:58:24AM A. Well, it functions in substantially the same way to achieve substantially the same result. And the function is that it releases 30 milligrams of doxycycline immediately on oral administration to alter subject's steady state blood levels. And the way it does it is about 8 milligrams of doxycycline in the DR portion is intentionally and immediately released by Lupin's thin and weak enteric coat. The result of all this is that their ANDA product functions as a 30 milligram IR 10 milligram DR in the body that is equivalent to Oracea.

THE COURT: Can I ask? Is there anything done to pills to cause them to linger in the duodenum or jejunum or ilium longer than they otherwise would or do they all pass at roughly the same rate?

THE WITNESS: There are actual polymers, Your Honor, that can be added to the surface of either capsules or pellets that are what we call bioadhesive. And they tend to be some cellulose derivatives and some others. This is a poly methacrylic acid copolymer. There's some acrylic acid versions that are also bioadhesive.

THE COURT: It can be done but there's no reason to think that was done here.

THE WITNESS: Absolutely not, Your Honor. And generally, the idea if you want to slow things down, pellets are good because they tend to get into the folds of the intestinal tract. And if they're somewhat adhesive, they go slower. So

they never really suck onto the intestines; they'll just go slower.

THE COURT: Because the absorption rate for a lot of meds is higher earlier in the intestinal tract. You might want it to go slower.

THE WITNESS: So a big, big effort in the 1990s and early 2000s was bioadhesion and what they call gastro retentive dosage forms, there's a whole company formed on this, where the idea was to get the release so far high up you would hit all the absorption windows and get higher bioavailability. By and large, they have not succeeded. Mother nature is a lot smarter than we chemists are.

THE COURT: I don't know if it matters whether you're eating roughage or not.

THE WITNESS: Food is going to move things along.

BY MR. COCHRAN:

Q. Dr. Rudnic, in your opinion, does Lupin's product infringe this claim under the doctrine of equivalents?

A. Yes, it does.

Q. Let's move on to the next slide. What do they show here?

A. This is Claim 1 of the Chang 532 patent. Showing that it has a delayed release or DR portion wherein the drug consists of about 10 milligrams of doxycycline.

Q. And in your opinion, does Lupin's ANDA product infringe this claim element?

12:01:22PM A. It does because as I testified, I believe that 8 milligrams
12:01:28PM is released as an IR portion to join the 22 milligrams of IR
12:01:33PM pellets to be 30 milligrams of IR. In a 40 milligram dosage
12:01:38PM form, that leaves 10 milligrams. And what you see is that is at
12:01:43PM a time other than immediately following oral administration.
12:01:48PM Q. Have you formed an opinion on whether this claim element is
12:01:51PM met under the doctrine of equivalents?
12:01:53PM A. Yes.
12:01:54PM Q. What is that opinion?
12:01:55PM A. Is that it does infringe on the doctrine of equivalents
12:01:58PM because it is insubstantially different from a pharmaceutical
12:02:02PM composition containing 10 milligram DR portion.
12:02:05PM Q. Why do you say that?
12:02:06PM A. Well, it has the same function and substantially the same
12:02:10PM way to achieve substantially the same result. The function is
12:02:14PM that it releases 10 milligrams of doxycycline at a time other
12:02:18PM than immediately following oral administration and about 8
12:02:23PM milligrams of doxycycline in that what is called DR portion is
12:02:26PM intentionally and immediately released by Lupin's thin and weak
12:02:31PM enteric coat. This leaves 10 milligrams to be released at a time
12:02:34PM other than immediately following oral administration. The result
12:02:38PM of all this is that Lupin's ANDA product functions as a 30
12:02:43PM milligram IR 10 milligram DR product in the body that is
12:02:48PM bioequivalence to Oracea, an undisputed 30 milligram IR 10
12:02:53PM milligram DR product.

12:02:55PM Q. In your opinion, does Lupin's product infringe this claim
12:02:58PM element under the doctrine of equivalents?
12:03:01PM A. It does.
12:03:02PM Q. And --
THE COURT: We can skip 085 and 086.
12:03:03PM MR. COCHRAN: You read my mind, Your Honor.
12:03:07PM BY MR. COCHRAN:
12:03:12PM Q. Let's go to Slide 87. Dr. Rudnic, what have you shown here?
12:03:18PM A. So this is Claim 15. I mentioned before this is a method
12:03:21PM claim for treating rosacea which is a form of acne in a human if
12:03:28PM you consider the dependent Claim 16. And you can see that
12:03:32PM Lupin's ANDA product infringes literally and under the doctrine
12:03:35PM of equivalents. And the composition parts of that claim we have
12:03:40PM already discussed at length.
12:03:42PM THE COURT: It's the same for the methods as for Claim
12:03:47PM 1; correct?
12:03:48PM THE WITNESS: Yes, Your Honor.
12:03:49PM THE COURT: So the key here is going to be -- well,
12:03:53PM that's the end of the 532. And then on the 740, we can go
12:03:57PM straight to Slide 91. Your analysis on the 740 patent of the
12:04:03PM 30:10 ratio is going to be the same for the 740 as for the 532;
12:04:08PM correct?
12:04:09PM THE WITNESS: You are correct, Your Honor.
12:04:10PM THE COURT: And then your analysis of the function and
12:04:12PM the doctrine of equivalents on 93 is the same for the 740 and the

532?

THE WITNESS: You are correct, Your Honor.

THE COURT: And I don't know if there's anything you want to say about Slide 94 about the delayed release. Is this the same as what we saw earlier or do you need to say anything further about this?

THE WITNESS: It is the same, Your Honor.

THE COURT: 94, 95, 96, the gelatin, the excipients, the coatings. So there's the method claim is the same on the 740 and the 532; right?

THE WITNESS: Correct, Your Honor.

THE COURT: Was there anything else you needed to add about differences in the method claims or differences in the 740?

BY MR. COCHRAN:

Q. One quick question. Dr. Rudnic, if we can go back one second? This will be very quick. Go back to Slide 98. Can you remind us what Lupin's ANDA product is indicated for?

A. It's indicated for the treatment of rosacea.

Q. Thank you.

THE COURT: And rosacea is a kind of skin disorder, isn't it?

THE WITNESS: Sure. The most notable patient that suffers from rosacea is former President Clinton, Your Honor. So if you see Mr. Clinton, often his face is red. And a lot of people suggest that's because he's imbibing. It's not. It's

because he suffers from rosacea. Rosacea is a form of acne. It's really like little red dots in your skin which cause your face to look red. So doxycycline, like most of the tetracyclines at low doses, very low doses, has an antiinflammatory effect.

THE COURT: Does anyone understand why that is? Because people thought this was a subtherapeutic dose.

THE WITNESS: Well, it's a subtherapeutic dose for an antibiotic. But most antibiotics, almost all of them, amoxicillin and others, at the very lowest of their doses are somewhat anti-inflammatory. The problem is, if you were to give them every day for the rest of your lives, you would probably get a superinfection and resistant bacteria and all sorts of things.

THE COURT: You think the max level at 1.0 microgram seems to work?

THE WITNESS: It does. So you're maximizing over the course of a day the anti-inflammatory effect for rosacea but not triggering the antibiotic effect which as we know causes all sorts of problems.

THE COURT: Sorry. I know you crafted your direct examination very well and very carefully. Is there anything else you want to add?

MR. COCHRAN: No, Your Honor.

(Lunch break at 12:07 p.m.)

C E R T I F I C A T I O N

I certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter.

/s/ Bobbie J. Shanfelder

Bobbie J. Shanfelder, RDR, CRR

Official Court Reporter

Date: January 9, 2024

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